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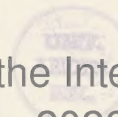
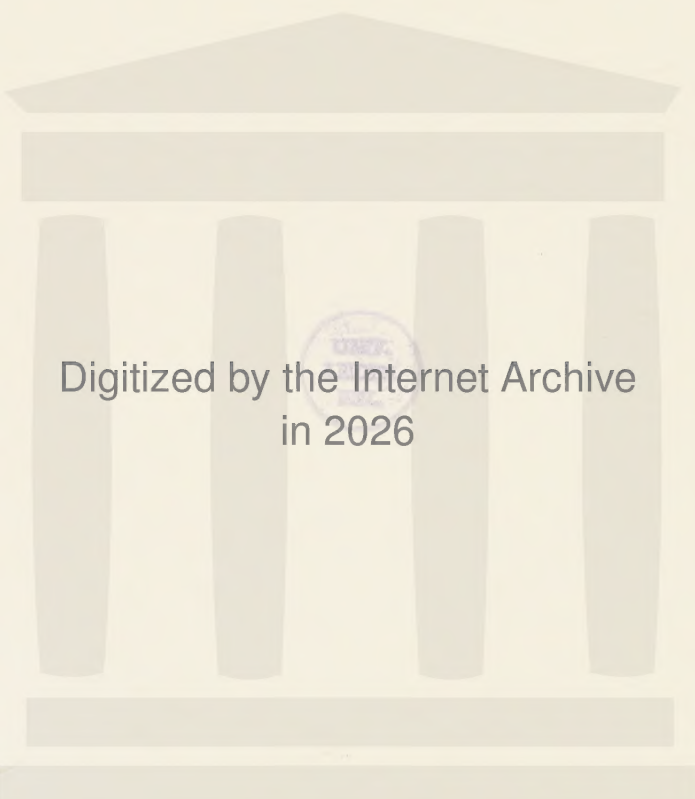
1986

COLORECTAL LIVER CANCER

Resection and regional chemotherapy



Henrik Ekberg



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Abstract Liver resection and various modes of regional chemotherapy for colorectal liver cancer were studied with respect to survival, complications and prognostic determinants. After liver resection major complications consisted of bleeding, infection and liver failure. The hypoalbuminemia was not treated but caused no problem. The absence of hypoglycemia was attributed to preoperative loading with parenteral glucose. Early hepatic recurrence and short survival was seen in patients with 4 or more colorectal liver metastases, extrahepatic disease, and a tumour-free margin of resection of less than 10 mm. Bilateral as compared to unilateral liver metastases did not have a demonstrable survival influence but had an increased risk of early hepatic recurrence. No factor was of any help in predicting the extrahepatic recurrence seen in half of the patients. Intra-abdominal relapse occurred in three quarters of the patients and in nearly all with recurrent disease after liver resection. In patients receiving hepatic arterial infusion of 5-FU, survival was negatively influenced by a large liver tumour volume, extrahepatic metastases, especially to the liver hilum, synchronous liver metastases, and single temporary dearterialization. Treatment morbidity was substantial, especially after combination with temporary dearterialization. Continuous intraperitoneal infusion of 5-FU via an implantable portal gave stable blood levels, low morbidity and excellent patient acceptance. These results have implications for selection of patients for liver resection, and help in designing chemotherapy trials in patients with nonresectable or resected colorectal liver secondaries.			
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 Lund University, S-221 85 Lund, Sweden.

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COLORECTAL
LIVER CANCER
Resection and regional chemotherapy

Henrik Ekberg
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Akademisk avhandling
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COLORECTAL

LIVER CANCER

Resection and regional chemotherapy

by

Henrik Ekberg

Lund 1986

To Marja, Andreas,
Turid and Kajsa.

The present thesis is based on the following papers:

I. MAJOR LIVER RESECTION - PERIOPERATIVE COURSE AND MANAGEMENT. H Ekberg, K-G Tranberg, R Andersson, B Jeppsson, S Bengmark.
Surgery (in press).

II. DETERMINANTS OF SURVIVAL IN LIVER RESECTION FOR COLORECTAL SECONDARIES. H Ekberg, K-G Tranberg, R Andersson, C Lundstedt, I Hägerstrand, J Ranstam, S Bengmark.
British Journal of Surgery (accepted for publication).

III. PATTERN OF RECURRENCE IN LIVER RESECTION FOR COLORECTAL SECONDARIES. H Ekberg, K-G Tranberg, R Andersson, C Lundstedt, I Hägerstrand, J Ranstam, S Bengmark.
World Journal of Surgery (accepted for publication).

IV. DETERMINANTS OF SURVIVAL AFTER INTRA-ARTERIAL INFUSION OF 5-FLUOROURACIL FOR LIVER METASTASES FROM COLORECTAL CANCER: A MULTIVARIATE ANALYSIS. H Ekberg, K-G Tranberg, C Lundstedt, G Hanff, J Ranstam, B Jeppsson, S Bengmark.
Journal of Surgical Oncology 31:246-254, 1986.

V. INTRAPERITONEAL INFUSION OF 5-FU IN LIVER METASTASES FROM COLORECTAL CANCER. H Ekberg, K-G Tranberg, B Persson, B Jeppsson, L-G Nilsson, T Gustafson, K-E Andersson, S Bengmark.
Journal of Surgical Oncology (accepted for publication).

In the text these papers are referred to by their Roman numerals.

CONTENTS

INTRODUCTION.....	6
Incidence.....	6
Natural history.....	6
Prognostic factors in untreated patients.....	7
Staging and grading.....	8
Liver resection.....	10
Perioperative course.....	10
Indications.....	11
Recurrence.....	13
Adjuvant treatment.....	14
Regional chemotherapy.....	15
Hepatic arterial infusion.....	15
Intraperitoneal infusion.....	18
Combined approaches.....	19
AIMS OF THE STUDY.....	21
MATERIAL AND METHODS.....	22
Patients.....	22
Management.....	22
Liver resection.....	22
Hepatic arterial infusion.....	23
Intraperitoneal infusion.....	24
Assay of 5-FU.....	24
Follow-up.....	24
Morphological data.....	25
Radiological data.....	25
Definitions.....	25
Statistical methods.....	26
RESULTS.....	27
I. LIVER RESECTION: PERIOPERATIVE COURSE.....	27
Mortality and morbidity.....	27
Bleeding.....	27
Infection.....	27
Liver failure.....	28
Laboratory values.....	28
Nutrition.....	28
II. LIVER RESECTION: SURVIVAL.....	28
Number of liver tumours.....	28
Intrahepatic spread.....	29
Extrahepatic disease.....	29
Resection margin.....	29
III. LIVER RESECTION: RECURRENCE.....	31
Sites of recurrence.....	31
Time to recurrence.....	31
Determinants of recurrence.....	31
Distribution of recurrence.....	34

IV. REGIONAL CHEMOTHERAPY: INTRA-ARTERIAL.....	34
Survival and response.....	34
Determinants of survival.....	34
Morbidity and mortality.....	37
V. REGIONAL CHEMOTHERAPY: INTRAPERITONEAL.....	38
Pharmacokinetics.....	38
Complications.....	38
Clinical effect.....	38
GENERAL DISCUSSION.....	39
I. LIVER RESECTION.....	39
Mortality and morbidity.....	39
Surgical technique.....	39
Bleeding.....	40
Infection.....	42
Laboratory values.....	42
Metabolic disorders.....	43
Determinants of survival and recurrence.....	44
Indications for liver resection.....	47
Sites of recurrence.....	48
Time to recurrence.....	49
Benefit of resection.....	49
II. REGIONAL CHEMOTHERAPY.....	50
Survival and response.....	50
Determinants of survival.....	51
Complications.....	53
Pharmacokinetics of IP infusion.....	56
Adjuvant treatment after liver resection.....	57
III. FUTURE ASPECTS.....	58
SUMMARY.....	60
REFERENCES.....	62

INTRODUCTION

Incidence

Colorectal carcinoma is the second most common cancer in Sweden, superseded only by breast cancer in women, and by cancer of the prostate in men (Cancer Registry 1982). In the United States cancer of the lung is more frequent in men, colorectal cancer being the third most common cancer with a frequency of 130,000 new cases each year (Cancer Statistics 1984). At present 4,300 new cases of colorectal cancer are clinically diagnosed in Sweden per annum. The frequency is slowly increasing, and the annual change in trend is 1%. About 15% of the patients are less than 60 years of age.

In autopsy series, more than half of patients dead from colorectal carcinoma have metastases in the liver (Pickren et al 1982). At the time of initial presentation 10% to 25% of patients have liver secondaries (Bengmark et al 1969, Cady et al 1970, Russel et al 1984). Colorectal resection with curative intent is performed in 60% to 70% of patients with colorectal cancer, and during the follow-up, liver metastases are diagnosed in 16% (5-26%) of the operated patients (Törnqvist et al 1982, Tong et al 1983, Gilbert et al 1984, Willet et al 1984).

Thus, the annual number of patients presenting clinically with colorectal liver cancer would be at least 1,000 in Sweden and 30,000 in the US. Treatment of these patients constitute a major clinical problem because of our limited knowledge of when and how they would benefit most from therapy.

Natural history

Survival after diagnosis of colorectal liver metastases is short in untreated patients and median survival rates are 6 to 18 months (Table 1). Time of detection depends on facilities and routines for diagnosis and follow-up, which may vary with time and between different hospitals. An increasing interest in liver surgery assisted by better diagnostic techniques for liver metastases, such as ultrasonography, CT, and CEA may have resulted in earlier diagnosis for some patients. Therefore, comparison between treatment results of today and earlier reports on the natural history are unreliable.

Recent prospective studies on the natural history of colorectal liver cancer are few and small. Today most surgeons regard it unethical to collect a consecutive series of patients with untreated colorectal liver metastases, because many patients would have resectable tumour and should be operated. In nonresectable disease, the benefit of

new treatment modalities should be evaluated in prospective randomized trials with an untreated control group. However, this idea is opposed by the fact that most surgeons and oncologists are unwilling to leave patients untreated.

Prognostic factors in untreated patients

The single most important factor influencing the length of survival in untreated patients with colorectal liver cancer is the extent of liver involvement (Table 1). Patients with solitary or few liver metastases and unilateral distribution have a substantially better prognosis as compared to patients with widespread disease. Wood et al (1976) found a mean survival of 3 months (6% 1-year survival) in patients with widespread bilateral metastases. Six patients with multiple unilateral deposits and 7 patients with a single

Table 1. Survival in patients with untreated colorectal liver metastases.

Authors	Extent of liver involvement	No.	Survival, mo.	
			median	mean
Jaffe et al (1968) *	All stages	60	6	-
Bengmark et al (1969) *	All stages	28	-	6
Cady et al (1970)	All stages	269	-	13
Baden et al (1975)	All stages	105	10	-
Weiss et al (1983)	All stages	10	18	-
Nielsen et al (1971)	Few	20	-	18
	Several	5	-	9
	Multiple	7	-	5
Wood et al (1976)	Solitary	15	-	17
	Several, one lobe	11	-	11
	Widespread, both	87	-	3
Wanebo et al (1978)	Solitary	18	19	19
	Multiple	149	7	10
Bengtsson et al (1981) *	< 25%, one lobe	12	6	-
	25-75%	5	6	-
	> 75%, both lobes	8	3	-
Boey et al (1981)	One lobe	20	9	-
	Both lobes	53	3	-
Wagner et al (1984)	Solitary	39	21	-
	Multiple, one lobe	31	15	-
	Widespread	182	10	-

* primary tumour not always resected.

metastasis were potentially resectable, and had a mean survival of 17 and 25 months, respectively. Similar survival rates were reported by Wagner et al (1984), and the difference in prognosis between solitary and multiple unilateral lesions in untreated patients was underscored by comparison of the 3-year survival rates, which were 21% and 3%, respectively.

Metastases in both liver lobes influence survival negatively in untreated patients (Wood et al 1976, Bengtsson et al 1981, Boey et al 1981, Wagner et al 1984). Correlation between bilateral disease and number of tumours, or liver tumour volume may account for part of this survival difference.

Lahr et al (1983) published a study on prognostic factors using a multifactorial analysis. Not only untreated patients were included: 41% received chemotherapy. Tumour localization into one or two lobes was a dominant prognostic variable, but when this and other factors were accounted for, the number of liver tumours did not influence survival significantly. In addition to intrahepatic spread, major prognostic factors were resection of the primary cancer, and serum levels of alkaline phosphatases, bilirubin and albumin.

The influence of laboratory findings and a nonresected primary was also demonstrated by Bedikian et al (1984) in a study on surgically incurable patients, who had liver metastases in 29%. It should be remembered that these patients presented with an advanced stage of colorectal cancer and were often (25%; Lahr et al 1983) unable to undergo resection of the primary tumour. The demonstrated prognostic factors are therefore relevant primarily in patients with advanced disease, untreated or given intravenous (IV) chemotherapy.

There are several other factors known to influence prognosis. In a study of 269 untreated patients with colorectal cancer and synchronous liver metastases, Cady et al (1970) found that presence of intestinal symptoms, enlarged liver preoperatively, ascites, advanced stage of the primary cancer, tumour extension to adjacent organs, peritoneal seeding or a nonradical operation for the colorectal cancer were factors, all adversely affecting survival.

Staging and grading

Prognostic factors in colorectal liver cancer have been used by several authors to classify the disease (Bengmark et al 1969, Parnes et al 1970, Bengtsson et al 1972, Wood et al 1976, Viret et al 1977, Pettavel & Morgenthaller 1978,

Fortner et al 1981, Gennari et al 1982). The aim has been to facilitate a reliable survival comparison in terms of natural history or treatment results.

Based on the experience that the extent of liver tumour is a major prognostic factor in untreated patients, Pettavel & Morgenthaller proposed a staging system in 1967. Initially, a sequence of variables was included, but after revision the authors (1978) presented a system based on the presence or absence of palpable hepatomegaly and elevated alkaline phosphatases. In untreated patients, variation in survival by stage of disease was presented. Laparotomy findings were used by Bengmark et al (1969) and Almersjö et al (1972) to estimate the tumour volume and to group the patients into I, less than 20%; II, 20% to 70%; and III, more than 70% of the liver replaced by tumour. However, the amount of tumour is, although the most important, only one variable among others influencing survival, and this has led to proposals of more complex staging systems.

In 1982, Gennari and coworkers proposed a staging system including percentage of liver involvement by tumour, single or multiple metastases, synchronous or metachronous, uni- or bilateral spread, infiltration of adjacent organs or structures, impairment of liver function, and presence or absence of liver cirrhosis. In patients subjected to liver resection, Gennari et al (1986) demonstrated that survival varied with the proposed stages of disease. The prognostic influence of the interval between bowel resection and detection of hepatic metastases was questioned and excluded in the authors' later report (Gennari et al 1986). There is also a lack of evidence that single or multiple metastases provide a preferred classification. Some authors have found multiplicity to influence prognosis significantly (Foster 1978) whereas many have not (August et al 1985a). Laboratory findings, especially alkaline phosphatases, are relevant for prognosis in untreated patients, but their influence in patients subjected to liver resection has not been documented. Extrahepatic disease, except for continuous tumour growth, was not included in the staging system.

In 1981, Fortner and colleagues suggested a staging system for liver disease defining stage I as tumour confined to the resected portion of the liver, stage II as regional spread including tumour rupture, direct extension of growth, histologically positive margin of resection or invasion of vessels and bile ducts, and stage III as extrahepatic disease. The prognostic discrimination by this classification was demonstrated in multivariate analyses (Fortner et al 1984 a,b).

A precondition for comparison of different reports or patient materials by stage of disease is that only one

staging system is used, but none has gained universal acceptance. Researchers are still not in agreement and one reason may be the difficulty to create a system complex enough to be reliable and yet simple enough to be widely used.

Evaluation of treatment results are fully reliable only in prospective randomized trials. Consideration of nontreatment prognostic factors should influence indications for treatment, or entry criteria and stratification in randomized clinical trials. However, assuming that treatment of liver metastases is effective to some degree, it follows that nontreatment prognostic factors will have a varying influence depending on the therapy. Therefore, prognostic factors will be further discussed below in connection with different treatments.

Liver resection

Perioperative course. Hepatic resection is presently the only treatment of colorectal liver metastases that offers hope for cure. Although it is now almost 100 years since the first reports on resective treatment of liver cancer (Garre 1888, Keen 1899), it is only in the past one or two decades that liver resection has become widely used. In recent reports (Table 2), operative mortality rates were up to 20%, and the incidence of postoperative complication ranged from 19 to 46%.

In 1971, Pinkerton and associates analysed the surgical management in relation to mortality and morbidity in a 15-year material comprised of 31 patients with liver cancer or trauma. Mortality was 25% in patients with neoplasm and 16 of 31 patients had major postoperative complications. A thoracoabdominal incision was frequently associated with pulmonary complications. Four of 8 patients with pneumonia died. Dissection and ligation of hilar structures were performed in 10 of 12 patients resected for tumour, and this technique was recommended without evidence of its superiority. The use of T-tubes for biliary decompression seemed to lead to increased mortality and morbidity. Gastrointestinal bleeding occurred in 5 patients, and 4 of them died. Infections such as subphrenic abscess and septicemia were common and resulted in one death. Antibiotics were given routinely in the postoperative phase. Two patients resected for liver tumour died in hepatic insufficiency. Other metabolic disorders included low levels of blood sugar and serum albumin. The authors recommended vigorous administration of albumin and total parenteral nutrition until the patient maintained adequate oral intake.

Table 2. Mortality and morbidity in liver resection

Author	n	mortality	morbidity
Liver tumour or trauma:			
Hanks et al (1980)	32	13 %	46 %
Ryan et al (1982)	52	8 %	46 %
Thompson et al (1983)	138	11 %	-
Iwatsuki et al (1983)	150	4 %	20 %
Liver cancer:			
Morrow et al (1982)	64	20 %	19 %
Cady et al (1979)	20	10 %	20 %
Balasegaram & Joishy (1981)	133	13 %	-
Tomas-de la Verge et al (1984)	64	5 %	31 %
Nims (1984)	10	0 %	40 %
Colorectal liver cancer:			
Logan et al (1982)	19	5 %	28 %
Adson et al (1984)	67	4 %	-
Fortner et al (1984a)	58	7 %	27 %
Kortz et al (1984)	16	6 %	43 %
Wagner et al (1984)	39	4 %	-
August et al (1985)	33	0 %	27 %
Coppa et al (1985)	25	4 %	28 %
Ghussen et al (1985)	19	11 %	37 %
Petrelli et al (1985)	36	14 %	-
Butler et al (1986)	62	10 %	26 %
Gennari et al (1986)	48	2 %	15 %

The recommendations by Pinkerton et al (1971) on management policy in liver resection does not seem to solve the problems. Recent reports indicate that major causes of operative mortality and morbidity (bleeding, infection and metabolic derangements) remain, and therefore, further analysis of the perioperative course in liver resection is warranted to refine the management of these patients.

Indications. According to Foster & Lundy (1981) and Adson (1981), liver resection for colorectal secondaries should be considered in patients with single or multiple metastases confined to one lobe of the liver and absence of tumour elsewhere. Taylor (1985) recommends resection only when the tumour is solitary, whereas Pilch & Barone (1984) advocate routine resection when merely a wedge excision would be sufficient. The reason why experienced authors reach different conclusions is that clearcut data for selection of patients with colorectal liver secondaries are limited, although the reports on the subject are numerous.

The number of tumours is one of the crucial factors in selecting patients for liver resection. In 1978, Foster reported a difference in 5-year survival rates for patients with resected solitary or multiple metastases (30% and 13%, respectively). Logan et al (1982) presented an impressive difference in actuarial survival (Table 3) for patients with single or multiple metastases. However, the study included only 12 patients with single and 7 patients with multiple metastases, and median follow-up of patients with solitary tumour was less than 2 years.

In a series by Adson and associates (1984), one quarter of the patients had multiple lesions, that were preoperatively believed to be solitary. The authors reported a reluctance to resect patients with multiple lesions, but the number of metastases in patients with multiple deposits was not stated. In a study by Butler and others (1986), most patients with multiple metastases had 2 and no patient had more than 4 lesions. This is relevant because there was no difference in survival between patients with single metastases and those with 2 or 3 deposits, in a report by August et al (1985a). These authors and Cady & McDermott (1985) demonstrated a significant prognostic discrimination by the number of tumours being more or less than 4. Whether this prognostic variable would remain significant in an analysis accounting for correlation with other factors has not been demonstrated.

There is only one published multifactorial analysis on prognostic factors in resected colorectal liver metastases (Fortner et al 1984a). Single or multiple deposits failed to discriminate for survival in the multivariate as well as in the single variable analysis. The stage of disease and Dukes' classification of the primary were the only significant factors demonstrated in the multiple regression

Table 3. The number of colorectal liver metastases related to survival after liver resection

Author	3-year survival (%)	
	single	multiple
Logan et al (1982)	83	0
Adson et al (1984)	40	38
Fortner et al (1984a)	41	50
Petrelli et al (1985)	44	11
Butler et al (1986)	53	37
	1, 2 or 3	4 or more
Cady & McDermott (1985)	55	0
August et al (1985a)	58	35

analysis. However, the stage of disease includes, as described above, several micro- and macroscopic factors determined intra- or postoperatively, and is therefore of no value for preoperative selection of patients.

Controversy remains about several other nontreatment factors influencing prognosis after resection. Bilateral metastases were shown by August et al (1985a) to influence survival negatively. However, this was not verified in the study by Butler et al (1986). Some have found the Dukes' classification of the primary cancer to be a discriminating indicator (Attiyeh et al 1978, Adson et al 1984, Fortner et al 1984a), whereas others have not (Morrow et al 1982, August et al 1985a). There is also disagreement on the influence of the interval between resection of the primary cancer and diagnosis of liver metastases. Attiyeh et al (1978), Morrow et al (1982), and Logan et al (1982) found that patients with synchronous metastases had a worse prognosis than those with metachronous lesions, but others disagree (Fortner et al 1984a, Gennari et al 1986). These discrepancies may be explained by variation in the number of patients or by concomitant influence by other prognostic factors.

Recurrence. Factors that influence survival may also influence the pattern of recurrence, including location and frequency of relapse and disease-free interval. Such information would further help in selecting patients for liver resection, because the aim of treatment is not only duration of survival, but also a disease-free life. There is no analyses on factors influencing recurrence after liver resection for colorectal metastases.

Several authors have reported on the pattern of recurrence after resection of the primary colorectal cancer (Table 4). In patients operated on with curative intent, sites of greatest risk of failure were the liver, the peritoneal cavity and the colorectal resection site. Intra-abdominal relapse alone dominated and occurred in 79% of patients with recurrent disease. Relapse in the liver-only occurred in 16%, whereas combined hepatic and extrahepatic recurrence was encountered in 46% of patients with progressive disease.

Reports on the sites of recurrence after resection of colorectal liver secondaries are limited to a total of 168 patients (Table 5). Including all patients, the incidence of hepatic or extrahepatic recurrence was 34% and 40%, respectively. Ninety-nine patients had relapse, and it may be calculated that one-third (31%) of these patients had recurrence in the liver-only, and two-thirds (69%) had extrahepatic failure (but the ranges were wide: 15-56% and 44-85%, respectively). The extent of intra- or extra-abdominal recurrence could not be assessed, because the specific sites of relapse were not always given.

Table 4. Sites of recurrence after primary colorectal resection *

Authors	n	intra-abd	hepatic only	hepatic	peri-toneum	resection site
Cass et al (1976)	105	74	13	-	6	62
Törnqvist et al (1982)	69	81	26	-	-	41
Tong et al (1983)	64	97	5	34	44	48
Gilbert et al (1984)	76	-	14	54	25	61
Russel et al (1984)	61	97	-	34	44	48
Willet et al (1984)	163	67	19	54	20	63
Sugarbaker et al (1985)	24	-	-	32	26	-
Total	562	79	16	46	26	56

* in percent of patients with relapse.

Table 5. Sites of recurrence after liver resection *

Author	n	Hepatic	Hepatic only	Extra-hepatic	Extra-hepatic only
Steele et al (1984)	13	23	23	77	77
O'Connell et al (1985)	18	67	56	44	33
Petrelli et al (1985)	20	75	15	85	25
Fortner et al (1984a)	18	39	28	72	61
Butler et al (1986)	30	67	33	67	33
Total	99	58	31	69	42

* in per cent of patients with relapse.

In summary, after primary colorectal resection, intra-abdominal failure dominates, and metastases in the liver-only are less frequent. After resection of liver secondaries, a combined hepatic and extrahepatic recurrence appear to be more frequent, whereas relapse in the liver-alone is less common. Whether or not the dominance of intraabdominal failure remains after liver resection should be clarified in further studies.

Adjuvant treatment. Data on sites of relapse after liver resection should form the basis for choosing between different adjuvant treatment modalities. Previous experience limited to some preliminary offered the patients 3 were given in 4 cycles for at least 6 portal or hepatic arterial catheter. No influence in

survival from the use of adjuvant treatment could be demonstrated. However, this was a nonrandomized and uncontrolled study and it does not allow for any substantial conclusions.

In a single-arm study with matched historical controls, O'Connell et al (1985) administered semustine in a single oral dose and 5-FU in IV injections for 5 days every 10 weeks. The authors were unable to demonstrate any evidence that this treatment was beneficial. August and coworkers (1985a) treated 21 of 33 patients with intraperitoneal infusion of 1,000 mg 5-FU daily for 5 days in 4-week cycles. There was no significant difference in survival between patients given chemotherapy and those who were not. However, the study was biased by uneven distribution of negative prognostic factors. Randomized, controlled trials are warranted, and for the design of these, the choice of treatment and factors for stratification, further studies on the pattern of recurrence after liver resection are needed.

Regional chemotherapy

Since the introduction of 5-FU in the 1950's, systemic chemotherapy has been used for treatment of colorectal liver metastases. Among the available cytostatic drugs today, 5-FU remains the most active single agent with an acceptable complication rate. The response rates for intravenous (IV) 5-FU are about 15%, but prolongation of survival has not been shown (Foster & Lundy 1981).

Lavin et al (1980) studied 1,314 patients with advanced colorectal cancer given one of ten chemotherapy programs. No significant difference in response or survival was observed, and none of the combined drug treatments was superior to 5-FU alone. In a prospective, randomized trial (Kemeny et al 1983), patients with advanced colorectal disease were treated with semustine, 5-FU and vincristine (MOF), or MOF and streptozotocin (MOF-Strep). The total response rate was 11% with MOF and 40% with MOF-Strep, but the difference in survival rates was not statistically significant. Consequently, the clinical value of a combined drug regimen in colorectal disease remains to be demonstrated.

Hepatic arterial infusion (HAI) chemotherapy was introduced in 1950 by Biermann et al and Klopp et al, but it was not until two decades later that the intrahepatic therapy gained considerable interest. Regional cytostatic administration to the liver allows for a higher hepatic drug concentration compared to the systemic concentration, and toxicity is reduced. Although HAI chemotherapy should be considered experimental, it is now widely used. Median survival in intrahepatic chemotherapy (Table 6) ranges from 3 to 12 months.

Table 6. Survival after hepatic arterial infusion chemotherapy in colorectal liver metastases

Authors mo.	Regimen	n	Median survival,
Watkins et al (1970)	Long-term FUDR	82	15
Cady & Oberfield (1974)	Long-term FUDR	51	11
Pettavel & Morenthaller (1978)	Long-term FUDR	57	10
Oberfield et al (1979)	Long-term FUDR	48	8
Petrek & Minton (1979)	3-week 5-FU	24	9
Reed et al (1981)	Long-term FUDR	88	10
Balch et al (1983)	2-week FUDR	81	12
Patt et al (1983)	5-day FUDR + mitomycin C	22	10
Weiss et al (1983)	2-week FUDR	17	13
Fortner et al (1984b)	Short-term FUDR	109	12
Niederhuber et al (1984)	2-week FUDR	50	18
Johnsson & Rivkin (1985)	2-week FUDR + cisplatin	40	13
Didolkar et al (1985)	Long-term 5-FU	30	17
Schwartz et al (1985)	2-week FUDR + mitomycin C	25	10

Some investigators have used historical "controls" for evaluation of treatment. Watkins and colleagues (1970) treated 82 patients who had colorectal liver metastases and median survival was 15 months after onset of symptoms. Eighty patients in a control group had a median survival of 4.2 months. The interval between onset of symptoms and start of treatment was 4.4 months, and consequently half of the treated patients should have been dead before receiving treatment if the two groups really had been identical in terms of prognosis. Contrary to the authors' claims, prolongation of survival after infusion therapy could be explained by selection of better risk patients.

In two studies a mathematical formula was used for prediction of survival and comparison with a "control" group. The formula was based on a multifactorial analysis of prognostic factors in 129 patients, untreated or given IV chemotherapy (Lahr et al 1983). Balch and associates (1983) reported an observed median survival of 12 months after onset of treatment, which was delayed for 14 months after diagnosis. In comparison, the predicted survival was 8 months after diagnosis. Niederhuber et al (1984) compared their survival results of 18 months after pump implantation with a predicted survival of 5.9 months from diagnosis,

although the interval between diagnosis and pump implantation was about 6 months. Consequently, it can be questioned whether or not the longer survival after HAI chemotherapy demonstrates the efficiency of the treatment.

These studies illustrate the fact that nonrandomized studies without untreated controls may lead to false conclusions in spite of elaborate efforts to avoid them. The main problem is selection bias, and this cannot entirely be solved by advanced statistical methods such as the multivariate analysis. Prognostic factors identified by multiple regression analysis may be transferable provided that all other variables are kept constant. The fact that the predicted survival was shorter than the delay before treatment is apparently caused by one or more negative prognostic factors, which were not evaluated and which occurred more frequently in "control" patients. The authors compared occurrence of some factors in treated and "control" patients, including the number of lesions. However, liver tumour volume was one of the variables not evaluated.

To date, there are only two completed randomized trials. Taylor (1978) reported on 24 patients given hepatic artery ligation (HAL) and HAI chemotherapy, or HAL with combined HAI and intraportal chemotherapy, or portal vein infusion alone, or no treatment. Combined arterial and portal infusion with HAL was associated with prolonged survival (mean 9.8 months as compared to 3.0 - 4.1 months in the other 3 groups). However, the impact of these results are restricted by the limited number of patients.

In 1979, Grage and others reported a randomized trial for IV versus intrahepatic 5-FU. Median survival was 13 months for IV and 10 months for HAI chemotherapy and there was no statistically significant difference. This study may be criticized mainly for two reasons. First, the regional chemotherapy was given as an induction course for 3 weeks only, and then all patients were treated intravenously. Second, there were only 61 patients, from six institutions, during a 5-year period. Response rates were 34% (HAI) and 23% (IV), and not significantly different. With this number of patients only a 40% difference would be detected (i.e. 25% versus 65%), and three times as many patients are needed to prove that a difference of 20% is statistically significant.

Randomized trials on intrahepatic versus systemic chemotherapy in colorectal liver secondaries are in progress. Two preliminary reports were recently published, but it is too early to evaluate the results (Lewis 1984, Kemeny 1984a).

In the absence of properly controlled studies, the treatment effect on survival cannot be evaluated. Patients are most often highly selected and the influence of nontreatment factors cannot be excluded in cases of long-term survival that are occasionally seen. An analysis of the determinants of survival after HAI of 5-FU is warranted, because a protocol for a randomized trial of HAI chemotherapy effect on survival should be based on knowledge of these factors.

Intraperitoneal infusion chemotherapy is in theory an attractive alternative to intra-arterial infusion. Compounds administered intraperitoneally are mainly absorbed through the portal circulation and a significant first-pass effect on the liver can be expected (Lukas et al 1971, Speyer et al 1981). IP administration of cytostatic drugs is not a new concept. In a theoretical paper, Dedrick et al (1978) reconsidered IP chemotherapy and provided a strong rationale for this form of regional therapy and guidelines in methodology. The concept was presented that ideal drugs for IP administration were those that pass slowly through the peritoneum and are rapidly cleared from plasma. A high concentration ratio between the IP fluid and the systemic circulation would be obtained.

Intraperitoneal administration has been examined for a number of cytostatic drugs, such as 5-FU (Collins et al 1980), methotrexate (Jones et al 1981), bleomycin (Bitran 1985), interferon (Rambaldi et al 1985), and others. The predominant indication for treatment has been advanced ovarian cancer, and there is no trial of the treatment effect in established colorectal liver cancer.

Sugarbaker et al (1985) treated 66 patients with either IP or IV 5-FU on days 2-5 of every month for a year after resection of colorectal primary cancer. Recurrence in the peritoneal surface occurred in 2 of 10 patients given IP infusion as compared to 10 of 11 patients given IV treatment. The difference in incidence of peritoneal carcinomatosis was highly significant, whereas disease-free interval or survival were similar in the two groups. The authors concluded that the natural history was markedly changed and that adjuvant IP treatment should be given to patients with a high risk for intraperitoneal recurrence, i.e. in perforated colon cancer, adjacent organ involvement or ovarian metastases.

In early trials, patients with malignant ascites were treated, and a variety of methodological problems arose, such as volume of infusion, catheter maintenance and evaluation of response (Speyer 1985). Reconsidering the use of IP chemotherapy, Dedrick et al (1978) recommended infusion of drugs by large volumes. Dunnick et al (1979) studied the dynamics of IP fluid, and found that a volume of

1,500 to 2,000 ml was needed to achieve a uniform distribution of agents infused.

The most frequently used technique for intraperitoneal administration includes the use of a percutaneous catheter. This has been associated with relatively frequent complications such as infection intra-abdominally or at the catheter exit site. The numbers of reported episodes of infection were 6 in 78 patients (Jenkins et al 1982) and 32 in 90 patients (Kaplan et al 1985). This complication is potentially avoidable using an implantable access device (Gyves et al 1984).

In summary, further studies on intraperitoneal infusion of 5-FU in patients with hepatic and/or other intra-abdominal colorectal secondaries are needed to refine the technique, evaluate the effect, obtain further pharmacokinetic data and thereby achieve the basis for a controlled trial.

Combined approaches

Hepatic artery ligation (HAL) results in necrosis of the central part of a liver tumour but leaves a peripheral zone of viable cells (Sparks et al 1975). Rapid development of hepatic collaterals counteract the effect of ligation (Bengmark & Rosengren 1970), and therefore a method of temporary occlusion was developed (Bengmark & Fredlund 1974). The aim of temporary dearterialisation adjunctive to HAI chemotherapy was to achieve central necrosis combined with oncolytic treatment of the tumour periphery. Survival effects and treatment complications of this combined therapy has not been sufficiently analysed.

Theoretically, the efficiency of hepatic arterial infusion can be improved by reduction of hepatic arterial blood flow. The drug concentration and the relative exposure of the hepatic tumour (and the liver) is inversely proportional to the blood flow rate through the infused artery at a constant dose rate (Ensminger & Gyves 1985). This can be achieved by arterial ligation, balloon catheters or occlusion by degradable microspheres. Dakhil (1982) used microspheres and found that the liver uptake of arterial BCNU was increased along with a decreased passage to the systemic circulation. Degradable microspheres containing mitomycin C were used by Kato et al (1981) to obtain release of the cytostatic drug at the same time as the arterial branches were blocked. A combination of blood flow obstruction and prolonged drug exposure may be achieved by the use of nondegradable microspheres loaded with releasable drugs (Morimoto et al 1981). Another approach is to inject the oily contrast medium Lipiodol which may result in a more selective exposure to the liver tumour (Nakakuma et al 1983). A maximum of drug delivery to the liver concomitant with a

minimum of systemic leakage may be obtained by isolated liver perfusion. A preliminary report by Aigner et al (1983) suggested that this approach is feasible in patients, however, the success of this method, as that of HAI chemotherapy, is limited by hepatotoxicity (Kemeny et al 1984b).

There are several trials combining external radiation of the liver and regional chemotherapy. None is randomized, many are not limited to colorectal liver cancer, and survival benefits remain to be evaluated. In one study (Friedman et al 1979), 21 patients were treated with radiation and intra-arterial 5-FU mainly because of colorectal cancer metastatic to the liver. The limiting toxicity was hematologic and 63% of the patients required transfusion during therapy. Barone et al (1982) reported a median survival of 8 months in 18 patients, and 2 patients died because of the therapy. In another study (Webber et al 1978), FUDR toxicity was apparently not enhanced by radiation treatment.

Internal radiation of the liver may be achieved by injection of radioactive microspheres. Grady (1979) treated 25 patients for liver cancer; 17 were regarded as responders and 3 died from treatment. The considerable mortality and morbidity makes the combined radiation and hepatic artery chemotherapy an investigative procedure and further studies are needed to evaluate its role in clinical practise.

AIMS OF THE STUDY

1. to study the intraoperative and postoperative course in patients undergoing liver resection in order to define factors that cause morbidity and mortality, and improve the management of these patients.

2. to study factors influencing recurrence and survival after liver resection for colorectal secondaries in order to obtain guidelines for the selection of patients and the choice of adjuvant postresective treatment.

3. to study morbidity and determinants of survival in hepatic intra-arterial infusion chemotherapy for nonresectable colorectal metastases, and to evaluate intraperitoneal infusion as an alternative method of regional treatment.

MATERIALS AND METHODS

Patients

In paper I, a consecutive series of 81 patients subjected to major liver resection for liver tumour was studied retrospectively. There were 34 men and 47 women with a median age of 59 (range 27-74) years. Seventy-four patients had malignant disease (hepatocellular carcinoma, 9; colangiocarcinoma, 8; mixed primary liver cancer, 3; colorectal liver metastases, 44; other liver secondaries, 10) and 7 patients had a benign liver tumour. None had liver cirrhosis.

In papers II-III, a consecutive series of 68 patients undergoing liver resection for metastases from colorectal cancer (1971-1984) was studied retrospectively. Thirty-four patients were male and 34 were female with a median age of 62 (range 27-76) years. Liver tumours were single in 34 (50%), unilateral in 52 (76%) and associated with extrahepatic disease in 12 (18%) patients. The median follow up time after liver resection was 20 (range 3-167) months and 53 patients (78%) had relapse after a median disease-free interval of 9 (range 1-36) months.

In paper IV, a consecutive series of 73 patients treated with hepatic arterial infusion (HAI) of 5-FU for colorectal liver metastases (1971-1981) was studied retrospectively. There were 37 men and 36 women with a median age of 59 (range 31-77) years. Twenty (27%) patients had extrahepatic disease including liver hilum lymph node metastases (15%) and lung deposits (11%). In 36 (40%) patients the tumour volume exceeded 50% of the liver volume.

In paper V, a prospective series of 9 patients with colorectal liver cancer treated with intraperitoneal (IP) infusion of 5-FU (1984-1985) was investigated. Four patients were male and 5 female, and the median age was 59 (range 45-73) years. Six patients had nonresectable liver secondaries at operation of the primary cancer, 2 developed liver recurrence after hepatic lobectomy and 1 received adjuvant treatment after extended right lobectomy. Except for the latter, all patients had extrahepatic disease.

Management

Liver resection (I). All patients received intravenous glucose (100 g) during the night before operation and 57 (70%) patients were given prophylactic antibiotics. Abdominal incisions only were performed in all patients; right- or leftsided transrectal incision was used in 62 (77%) patients. Ligation of hilar vessels and bile ducts to the resected lobe ("preresection ligation") was performed before

transection of the liver parenchyma in 29 (36%) patients. The remaining 52 patients were operated upon with the direct parenchymal approach. No clamping of the portal vein or hepatic artery was used. The liver transection was made bluntly and vessels were individually ligated or cuterized. No mattress sutures were used.

Routinely, fresh frozen plasma was administered after transfusion of every third unit of whole blood or erythrocyte concentrate. Two to 4 units of platelet concentrate were given after the first 6 units of blood, and additional platelets were given when the platelet count was less than 60,000. Albumin or plasma was not routinely used and was given only in conjunction with massive transfusion of blood. Postoperative nutrition consisted of intravenous, hypocaloric glucose administration and start of oral intake within a few days. Total parenteral nutrition was not routinely used.

In papers II and III, management of patients undergoing liver resection was identical to that described above.

Hepatic arterial infusion (IV). Patients with nonresectable colorectal liver metastases were selected for HAI chemotherapy provided the patient had only minimal or no extrahepatic disease and was in good general condition. The primary cancer had been excised in all cases and no patient showed signs of local recurrence at the start of regional chemotherapy. The median interval between diagnosis and start of treatment of liver metastases was 2 (range 0.4-21) months. Regional infusion of 5-FU was given either on a long-term (500 mg 5-FU per day for 3 months with 6 months interval, start to start) or a short-term (1000 mg per square m body surface per day for 5 days every 6 weeks) basis. Chemotherapy was administered via a catheter introduced surgically in 40 (55%) patients and percutaneously (through the left brachial artery, if possible) in 21 patients. Patients with more than one artery supplying the liver always underwent laparotomy for ligation of accessory arteries. An operatively placed catheter was preferred for patients undergoing long-term chemotherapy. In most cases, the choice between long-term and short-term infusions was arbitrary.

Long-term infusion was preceded in 21 patients by a single temporary dearterialization. Laparotomy was performed and collaterals to the liver were divided. The proper hepatic artery was isolated and two loops of thin teflon catheters were placed around the vessel, one on each side of the gastroduodenal artery, and brought out through the abdominal wall. An infusion catheter was introduced into the hepatic artery from the gastroepiploic or gastroduodenal artery. Single occlusion of the hepatic artery for 16 hours was

performed a few days after operation and intra-arterial infusion of 5-FU was started subsequently.

Intraperitoneal infusion (V). An intraperitoneal access device (Travenol Europe, Brussels) was implanted under general anaesthesia. The portal was fixed to the fascia in a subcutaneous pocket, lateral to the rectus abdominis muscle, and the silicone catheter was introduced into the abdomen via a subcutaneous tunnel to the midline. Antibiotic prophylaxis was administered shortly before and during the operation. All handling of the insertion site and external catheters was done with a strict aseptic technique and the dressing was left unchanged during the 5-day infusion period.

Before every course of chemotherapy, a nuclear scan with intraperitoneal 99m-Technetium sulfur colloid (TcSc) was performed in order to ensure distribution to the entire peritoneal cavity. If distribution was limited, intraperitoneal infusion without 5-FU was started. Repeat TcSc scans were done 2 and 24 h later, and the infusion with 5-FU was started if any of these demonstrated complete intraperitoneal distribution.

1500 ml of lactated Ringers solution was infused into the peritoneal cavity over 90 min. Subsequently, a lactated Ringers solution containing 1 g of 5-FU and 500 IU of heparin per 1000 ml was infused. The solution was given by constant, continuous infusion at a rate of 42 ml/h (1000 ml/d) for 5 days and repeated every 6 weeks. Criteria for discontinuation of treatment consisted of complications caused by therapy or progressive disease.

Assay of 5-FU

5-FU was measured by a modification of earlier described liquid chromatography methods (Hornbeck et al 1981, Sampson et al 1982). In order to study the stability of 5-FU in whole blood, 4 samples were divided into 3 portions and incubated at different temperatures: 37 °C, 25 °C, and in an ice-water mixture. After various times, aliquots were taken and blood and plasma concentration of 5-FU were analysed. Stability of 5-FU in plasma was studied in a similar manner.

Follow-up

The follow-up after liver resection of colorectal secondaries (III) was standardized and based on clinical examination with rectoscopy and laboratory tests, including liver function tests and carcinoembryonic antigen (CEA), after 3, 6, 9, 12, 18, and 24 months and then at yearly intervals. Barium enema and/or colonoscopy and X-ray of the

lungs were performed routinely after 1, 3, and 5 years. When clinical or laboratory investigations suggested liver metastases, scintigraphy, ultrasonography and/or CT combined with fine needle biopsy were performed. Other investigations, such as bone scintigraphy and CT of the pelvis, were carried out only when symptoms or laboratory findings indicated recurrent disease. In 23 (34%) of the patients extent of recurrence was determined not only by clinical, laboratory and radiological investigations, but also by laparotomy findings at the time of initial relapse.

Patients subjected to intra-arterial chemotherapy were examined every 3 months, that is at start and end of every long-term cycle or after every second short-term cycle. The follow-up included physical examination, pulmonary X-ray, and hepatic angiography with catheter patency control and liver tumour volume estimation.

Evaluation of intraperitoneal treatment effect on hepatic metastases was performed after every 2 cycles of therapy (i.e. every 3 months). It was based on clinical examination and CT scan and/or ultrasonography of the liver.

Morphological data

All histopathology of colorectal and liver disease was reviewed. In papers II-III, data on the number and size of the liver metastases were taken from histopathology and/or laparotomy findings. Data on the tumour-free margin of the resected liver specimens were evaluated by histopathology. Recurrent disease after liver resection was usually morphologically verified. However, metastases to the lungs and bone were diagnosed in some patients by radiology only.

Radiological data

As part of the diagnostic work-up before treatment (liver resection or hepatic arterial infusion) angiography of the liver was performed. In papers II-IV, the entire radiological material was reviewed. The extent of liver involvement, in per cent of total liver volume, was estimated and the patients divided into 4 groups: less than 25%, 25-49%, 50-74%, and 75% or more. The vascularity of the metastases were also evaluated, and subjectively classified as low, moderate or excessive.

Definitions

Treatment (operative) mortality: death within one month or before the patient left hospital.

Survival: Interval from liver resection or start of chemotherapy until death. Survival times are actuarial.

Response: Partial response - decrease in liver tumour volume evaluated on angiography, compared with the examination at the start of treatment, and with a duration of at least 3 months. The extent of decrease in liver tumour volume was not specified. Stable disease - stationary tumour volume for at least 3 months.

Size and number of metastases: Tumours were classified as "small" when the largest diameter was < 4 cm and as "large" when it was > 4 cm. The term "multiple" signifies 2 or more tumours as opposed to 1 ("single"), whereas "solitary with satellites" denotes a large tumour closely surrounded by one or more small tumours in the same segment of the liver. The term "multiple large" denotes that at least one of the tumours had a diameter of ≥ 4 cm.

Statistical methods

Mann-Whitney rank sum test, Spearman rank correlation coefficient, chi-square test and analysis of covariance were used when appropriate. Factors of possible influence on survival (II,IV) and recurrence (III) were tested separately in single-variable analyses using the generalized Wilcoxon test (Lee & Desu 1972). Curves of survival or recurrence were constructed with the life-table technique. Prognostic factors were tested simultaneously using the multivariate analysis, Cox proportional hazards model, applied in a stepwise manner (Kalbfleish & Prentice 1980).

RESULTS

I. LIVER RESECTION: PERIOPERATIVE COURSE

Mortality and morbidity

Operative mortality was 4.9% and occurred after right-sided resections only. Bleeding from the caval vein associated with technical difficulties led to 1 intra-operative death and 1 death 11 days after operation. Another patient died because of necrosis of the remnant part of the liver 2 weeks after surgery. One patient was reoperated twice because of intraabdominal abscess and succumbed due to gastrointestinal bleeding 6 weeks after extended right lobectomy.

Fourteen (17%) patients had major complications including bleeding and/or infection (10%) and overt liver failure (2%). A total of 27 (33%) patients had postoperative complications, and all except 3 patients had been operated with right or extended right lobectomy.

Bleeding

The amount of blood transfused increased with the amount of liver resected; median 2.5 (range 1-9) units of blood for left lateral segmentectomies and 12 (range 5-42) units for right lobectomies. The direct parenchymal approach was associated with a shorter operation time as compared to preresection ligation (4.6 vs 5.7 h; $p < 0.001$), but there was no difference in intraoperative bleeding, or postoperative complication rate comparing the two techniques in patients subjected to right or extended right lobectomies. The postoperative hospital stay varied with the amount of blood transfused ($r_s = 0.58$; $p < 0.001$) and with the operation time ($r_s = 0.48$; $p < 0.001$).

Thrombocytopenia was pronounced after operation and was associated with the number of blood transfusions. The relative decrease in platelet count (1st day postoperative value in per cent of the preoperative value) varied with the amount of blood transfused ($r_s = -0.60$; $p < 0.001$). After 10-15 units transfused, the platelet count was reduced to 50% of the preoperative value.

Infection

Five patients were reoperated because of a proven abscess. In another 5 patients, a suspected intraabdominal abscess could not be verified at laparotomy, which revealed some accumulation of bile in 3 and normal findings in 2 patients. All patients with postoperative infection had received prophylactic antibiotics.

Liver failure

Fulminant liver failure complicated the course in 2 patients. It was associated with necrosis of the remnant part of the liver in one the patients who died. The cause of necrosis was not clarified at autopsy, but it may be relevant that the patient was operated with the preresection ligation technique. The second patient was deeply jaundiced preoperatively in spite of transhepatic drainage and was subjected to extended right lobectomy (85%) because of a liver hilum cholangiocarcinoma. The liver coma was treated immediately and reversed after 3 weeks of intensive therapy including plasmapheresis and administration of solutions enriched by branched chain amino acids. The therapy had impressive effects on blood levels of ammonia, bilirubin, liver enzymes, and amino acids.

Laboratory values

Liver enzymes were markedly changed during the first postoperative week. A sharp rise of transferases (alanine aminotransferase and aspartate aminotransferase) normalized within a week. Transferases were significantly more increased after right lobectomies as compared to left-sided resections during the first 2 postoperative days ($p < 0.001$ and $p < 0.05$, respectively). Bilirubin, which increased rapidly and returned slowly in all patients, was also found to be higher after right lobectomies, and significant differences were found during the first 5 days postoperatively ($p < 0.01$ at all time points). Levels of alkaline phosphatases and γ -glutamyltransferase showed an initial moderate decline and then increased to normal within the first week. The decrease in alkaline phosphatases was more profound when the preoperative value was above normal ($r_s = -0.74$, $p < 0.001$).

Nutrition

Blood glucose levels were stable during and after operation, and no episodes of hypoglycemia were encountered. Serum albumin showed an immediate and moderate fall and did not start to rise significantly during the first week. This did not appear to have any adverse effects.

II. LIVER RESECTION: SURVIVAL

Number of liver tumours

Half the patients had multiple liver metastases and a shorter survival than patients with a single tumour ($p < 0.05$). However, when considering only patients with unilateral disease, multiplicity did not influence prognosis significantly ($p = 0.11$).

The 3- and 5-year survival rates after resection of a single metastasis were 45% and 24%, respectively. For patients with less than 4 tumours, the figures were similar, 41% and 20% (Fig. 1), whereas none of the patients with 4 or more tumours survived 3 years ($p=0.03$).

Ten patients had "solitary" metastases with satellites, and their median survival after resection was 16 months, none of them surviving 3 years. This was significantly worse than the survival for truly solitary metastases (median 27 months; $p=0.01$).

Combining the number and size (more or less than 4 cm) of the tumours, it was found that patients with a small single metastasis had the best prognosis with a 5-year survival rate of 40% and a significantly longer survival than those with multiple small metastases.

Intrahepatic spread

A quarter of the patients had bilateral metastases, most of which were tiny on one side and resected with wedge resection combined with lobectomy on the contralateral side. Patients with unilateral disease had a 3-year survival rate of 37%, as compared to 18% for those with bilateral metastases. However, the 5-year survival rates were nearly identical, and the tendency towards a better prognosis for unilateral disease was not significant ($p=0.14$).

If only patients with less than 4 tumours were considered, there was no statistically significant difference in prognosis for unilateral or bilateral disease, and the 5-year survival rates were the same (20%).

Extrahepatic disease

Extrahepatic metastases had a great negative influence on survival (Fig. 2). None of the patients with extrahepatic metastases in the liver hilum lymph nodes ($n=6$) or elsewhere ($n=6$) survived 3 years. In comparison, the 3-year survival rate was 25% in patients with a benign biopsy of liver hilum lymph nodes ($n=24$) and 36% in patients with liver-only disease ($n=56$).

Resection margin

Patients with a histologically positive margin of resection had a poor prognosis with no 3-year survivors. A tumour-free margin of less than 10 mm was not substantially better (6% 5-year survival), however, with a margin of more than 10 mm, survival was significantly improved (29% at 5 years).

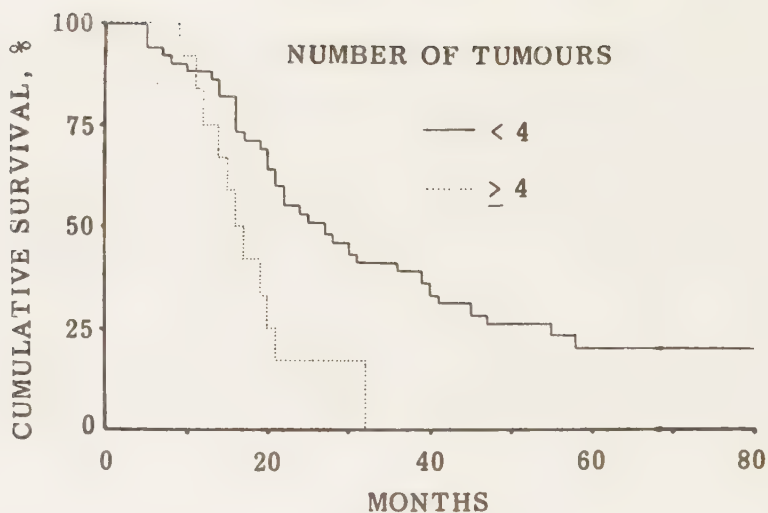


Fig. 1
 Liver resection. The difference in cumulative probability of survival between < 4 (—, $n=55$) and ≥ 4 liver tumours (... , $n=13$) was significant ($p=0.03$).

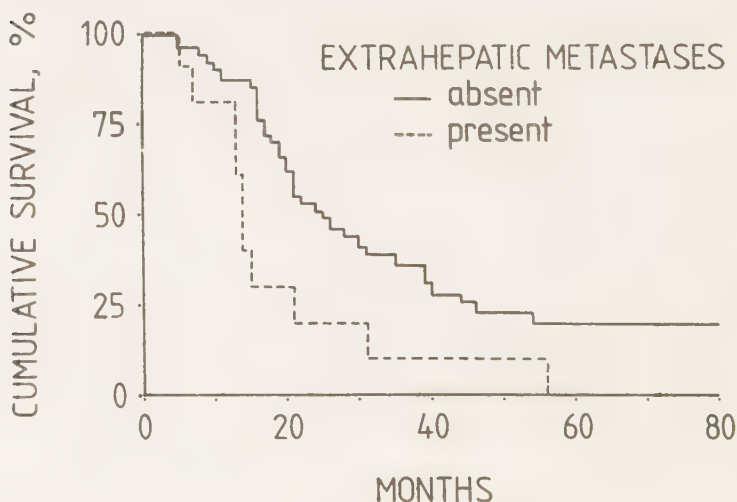


Fig. 2
 Liver resection. Cumulative probability of survival in patients with extrahepatic metastases (... , $n=12$) and without (—, $n=56$) extrahepatic disease. The difference in survival was significant ($p<0.01$).

In summary, the predominant adverse determinants of survival were presence of 4 or more metastases, extrahepatic disease and less than 10 mm tumour-free resection margin. This was confirmed in the multivariate analysis, and for each variable the risk of short survival was doubled ($p < 0.05$). No other factor was found to decrease the chance of survival significantly, including classification of the number of tumours into single or multiple. Other variables that did not significantly influence prognosis were site of the primary cancer, Dukes' classification and differentiation of the primary tumour, synchronous or metachronous disease, type of liver resection, uni- or bilateral disease, liver tumour volume, and tumour size.

III. LIVER RESECTION: RECURRENCE

Sites of recurrence

Fifty-three (78%) of 68 patients had recurrence. The liver, lungs and peritoneal cavity (intraabdominal nodes or peritoneal surface) were most frequently involved and all patients with relapse had recurrence at one or more of these sites. Fifty (74%) patients (94% of those with relapse) had intraabdominal recurrence; in the liver, peritoneal cavity or at the colorectal resection site. The liver was affected in 44 (65%) patients and solely in 19 (28%) patients. Extrahepatic metastases were encountered in 34 (50%) patients and were unassociated with liver recurrence in 9 (13%) patients. The lungs were the most common site of extrahepatic recurrence and were affected in 15 (22%) patients. Three patients had pulmonary metastases only.

Eight (12%) patients had recurrence at the site of bowel resection, and 5 of them had liver metastases synchronous with the primary cancer.

Time to recurrence

The median disease-free interval in all patients was 11 (1-36) months after liver resection, and in patients with recurrence the interval was 9 (1-36) months. Relapse in the liver was diagnosed within a year in 68% of the patients and within 2 years in 89%. Lung metastases occurred within a year in 33% and within 2 years in 67%.

Determinants of recurrence

Disease-free interval after liver resection was short if there were multiple liver tumours, and especially if the number of liver tumours was 4 or more. Bilateral hepatic disease was accompanied by an earlier recurrence than unilateral disease. The difference was reduced, but still significant, when patients with multiple metastases only

(n=34) were considered (median 5 and 12 months, respectively; $p < 0.05$). A similar difference was seen also in patients with < 4 tumours although the 3- or 5-year disease-free rates were only slightly higher in unilateral than in bilateral disease ($p=0.04$).

The extent of liver involvement by tumour influenced the disease-free interval, especially when the liver involvement was 50% or more. Patients operated with wedge resection had a longer disease-free interval than the other patients. A tumour-free margin of < 10 mm as well as absence of extrahepatic metastases, including those in the liver hilum lymph nodes, was of great importance.

The following variables did not show any statistically significant variation with disease-free interval or time to hepatic recurrence: site of primary tumour, Dukes' classification, histologic differentiation of the primary, synchronous or metachronous metastases and liver tumour size.

Table 7. Determinants of recurrence
(Cox proportional hazards model, n=68)

Status	Recurrence.....					
	Any site, Relative risk *	p	Hepatic, Relative risk	p	Extrahepatic, Relative risk	p
Extrahepatic disease	3.9	0.0005	3.0	0.003	5.6	0.0006
Type of operation, major resection	3.3	0.01	3.0	0.003	n.s.	
<u>> 4</u> liver tumours	2.8	0.005	3.1	0.002	n.s.	
Resection margin, < 10 mm	2.4	0.02	4.2	0.0002	n.s.	
Bilateral spread	2.0	0.03	2.0	0.03	n.s.	
Liver tumor volume, <u>> 25%</u>	2.0	0.06	1.9	0.06	n.s.	

Included are variables with $p < 0.25$.

* A Relative Risk > 1 means that a patient with the Status above has a correspondingly greater risk of recurrence than a patient with the negation of the Status, provided that all other variables in this analysis are kept constant.

The results of the multivariate analyses agreed with those of the single variable analyses, and are shown in Table 7. The following variables were associated with early recurrence: extrahepatic disease, major liver resection, number of tumours being ≥ 4 , resection margin of < 10 mm, bilateral intrahepatic spread and liver tumour volume $\geq 25\%$. Each variable increased the risk of recurrence 2-4 times. If the number of tumours was classified as single or multiple, instead of < 4 or ≥ 4 , liver tumour number did not significantly affect disease-free interval. It is noteworthy that major liver resection, as compared to wedge resection, was accompanied by earlier recurrence also in this analysis.

The multivariate analysis was repeated for hepatic recurrence (Table 7). The outcome was almost identical with the exception that the resection margin and the number of tumours were the two most important risk factors. In the multivariate analysis for extrahepatic recurrence, the presence of extrahepatic disease before resection increased the risk of relapse. No other variable could be demonstrated to vary with the risk of extrahepatic recurrence.

Table 8. Distribution of recurrent disease.

Variable	Hepatic	Extra-hepatic	Total
Number of hepatic tumours			
< 4	56 **	53	73 *
≥ 4	100	38	100
Extrahepatic disease			
not present	57 **	46	73 *
present	100	67	100
Resection margin			
> 10 mm	48 *	52	67
≤ 10 mm	76	49	85
Type of operation			
Wedge resection	46	54	62
Major resection	69	49	82
Intrahepatic spread			
Unilateral	60	50	75
Bilateral	81	50	88
Liver tumor volume			
$< 25\%$	66	43	71
$\geq 25\%$	63	56	89
Total	65	50	78

Figures are percentages. * = $p < 0.05$; ** = $p < 0.01$ (chi-square test).

Distribution of recurrence

The distribution of progressive disease related to the demonstrated determinants of recurrence is shown in Table 8. Patients with less than 4 liver tumours, no extrahepatic disease or a resection margin of less than 10 mm had a low frequency of recurrence in the liver. (Type of operation varied with liver-only recurrence: wedge resection 8% and major resection 33%, $p < 0.05$). However, none of the variables was related to the frequency of extrahepatic relapse.

Forty-five patients had less than 4 tumours and no extrahepatic disease. Twenty-one (47%) of these patients had hepatic recurrence as compared to 23 (100%) of the remaining patients ($p < 0.001$). Development of extrahepatic metastases, however, was equally frequent in both groups, 49% and 52%, respectively.

IV. REGIONAL CHEMOTHERAPY: INTRA-ARTERIAL

Survival and response

The overall median survival time was 11 (1-73) months from date of treatment initiation. Survival was 42% after 1 year, 10% after 3 years and 5% after 5 years.

Twenty-six patients (36%) showed partial response with a median duration of 6 (3-25) months. Tumour volume was stationary in 9 (12%) patients with a duration of 7 (3-21) months. Regression or stationarity of disease was consequently noted in 48% of the patients, and median survival was 21 (3-73) months for responders as compared to 7 (1-24) months for nonresponders ($p < 0.0001$).

Determinants of survival

In the multivariate analysis, nontreatment variables significantly increasing the risk of short survival included presence of lymph node deposits in the liver hilum, increased liver tumour volume, short interval between diagnosis of primary cancer and liver metastases, and elevated bilirubin or alkaline phosphatases (Table 9). Accordingly, in the single variable analyses, extrahepatic metastases (Fig. 3) and liver tumour volume (Fig. 4) had a great impact on survival. However, the disease-free interval, dicotomized as synchronous or metachronous liver metastases, did not vary with survival.

Number of liver tumours, degree of vascularisation, histologic differentiation and Dukes' classification of the primary tumour were variables without statistical significant influence on survival.

Table 9. Determinants of survival
(Cox proportional hazards model, n=71)

Variable	Status 1 vs 2	Relative Risk 1:2 *	p
<u>Non-treatment variables</u>			
Lymph node metastases in liver hilum	yes vs no	8.4	0.0006
Liver tumour volume	>75% vs <25%	8.3	0.002
Bilirubin, $\mu\text{mol/l}$	40 vs 20	7.1	0.002
Interval primary op.- liver metastases, mo.	0 vs 12	2.4	0.0001
ASAT, $\mu\text{kat/l}$	0.7 vs 1.4	1.9	0.02
ALP, $\mu\text{kat/l}$	9.2 vs 4.6	1.6	0.001
<u>Treatment variables</u>			
Temporary deart.	yes vs no	7.7	0.001
Partial hepatic thrombosis	no vs yes	5.4	0.0001
Infusion cycle	short vs long	3.5	0.02

* A relative risk 1:2 > 1 means that a patient with status 1 has a correspondingly greater risk of short survival than a patient with status 2, provided that all other variables included are kept constant.

Treatment factors with positive influence on survival included hepatic arterial thrombosis and long-term infusion cycle (as compared to short-term) according to the multiple regression analysis (Table 9). Temporary dearterialisation had a negative impact on prognosis. When variables were tested separately, similar results were obtained. Excluding patients with temporary dearterialisation, long-term regional infusion was accompanied by a significantly better prognosis than short-term infusion ($p < 0.05$).

When partial response/stationary disease was entered into the multivariate analysis, a significant influence on survival was found, and there were only slight changes of the other risk factors in Table 3. Nonresponders carried a relative risk of 4.5 ($p < 0.02$) for a short survival.

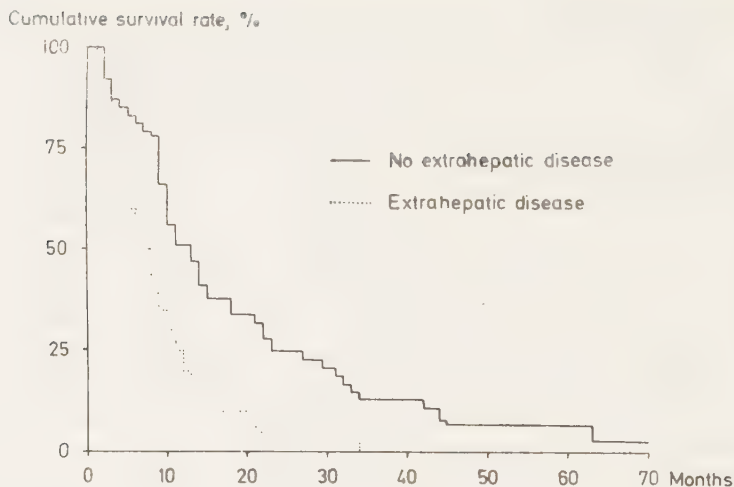


Fig. 3.
HAI chemotherapy. Cumulative survival for patients with extrahepatic metastases (..., n=20) was significantly shorter ($p < 0.01$) than that for patients without extrahepatic metastases (—, n=53).

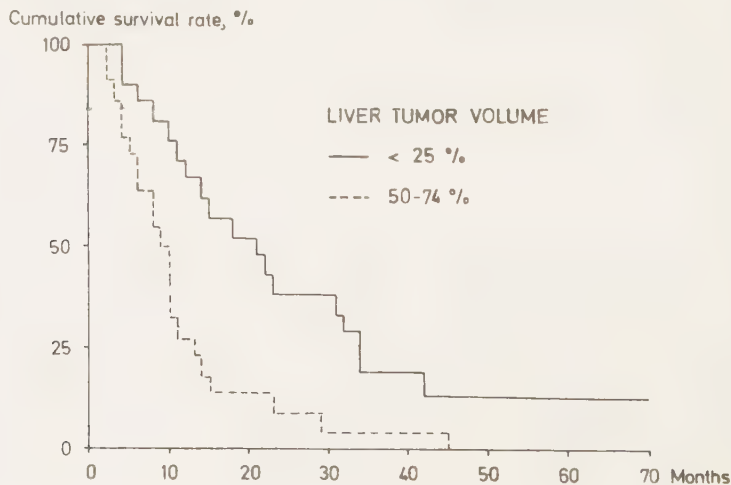


Fig. 4.
HAI chemotherapy. Cumulative survival according to liver tumour volume. The difference between < 25% (—, n=21) and 50-75% (---, n=26) was statistically significant ($p < 0.001$).

**Table 10. Complications after catheterization alone (n=23)
and addition of temporary dearterialization (n=21)**

	Catheter alone		Temporary deart.	
	n	%	n	%
Mortality	-	-	2	10
Intrahepatic abscess	-	-	3	14
Subphrenic abscess	-	-	1	5
Subcutaneous abscess	1	4	-	-
Bleeding	-	-	2	10
Aneurysm	2	9	7	33
Total no. of patients	3	13	9	43

Morbidity and mortality

Complications to treatment are listed in Table 10. Serious postoperative complications occurred almost exclusively in patients subjected to temporary dearterialisation. Two patients belonging to this group died before leaving hospital, giving a mortality rate of 10% for temporary dearterialisation. One of the patients died in generalized disease 2 months after treatment, and the other was reoperated twice because of subphrenic abscess and died in connection with the last operation. Two of 3 patients with intrahepatic abscesses were reoperated for drainage. Surgery was also performed in 2 patients with subphrenic or subcutaneous abscess.

Catheter related problems occurred in about half of the patients, and were mainly composed of dislocation of the catheter, pump failure, blockage or bleeding at the insertion site. Two patients were reoperated because of bleeding from the gastroduodenal artery. In another 2 patients, reoperation was performed because of hepatic artery aneurysm, which was seen after temporary dearterialisation in 7 patients. The catheter perforated the duodenum in 2 cases and sepsis occurred in 1 patient. Partial or total thrombosis of the common hepatic artery or its two main branches was seen in 43 patients (59%). As a rule, thromboses were seen early and occurred in median 11 (range 1-70) weeks after start of treatment. The brachial artery thrombotized in 18 (40%) of 45 patients receiving infusion via a percutaneous catheter.

Systemic cytotoxic reactions were not seen in patients treated with regional infusion alone. Thrombocytopenia or leucocytopenia was the reason for dose reduction in 9 (12%) and 8 (11%) patients, respectively, given triple and/or intravenous 5-FU treatment after discontinuation of regional infusion. Abdominal discomfort, loss of appetite or diarrhea were complaints from 30% of the patients. Signs of chemical hepatitis were difficult to distinguish from progression of the liver malignancy. In patients showing partial response or stable disease, no instances of elevated liver function tests as a sign of liver cell damage were noted in connection with therapy.

V. REGIONAL CHEMOTHERAPY: INTRAPERITONEAL

Pharmacokinetics

The steady-state systemic plasma 5-FU concentration was 0.56 ± 0.04 (mean $\pm$ SEM) $\mu\text{mol/l}$ with a coefficient of variation of $25\% \pm 3\%$. The apparent total body clearance (TBC) was 10.0 ± 0.7 l/min. There was a small but significant increase in steady-state during the period of infusion ($0.04 \mu\text{mol/l}$; $p < 0.01$). No difference in morning and evening values was found.

The blood and plasma levels of 5-FU were unstable; after incubation of blood samples for 1h at 37°C , 5-FU fell to 46% of its initial value, and a half-life of 57 min was calculated. After incubation of plasma in 37°C for 4h, the decrease was less than 5%.

Complications

Patient acceptance was excellent. Infection occurred in none of the patients. Chemotoxicity was minimal and no evidence of systemic toxicity was found. Six patients had slight abdominal discomfort with tenderness and distention during the week after treatment. In one patient chemical peritonitis led to discontinuation of therapy. The initial TcSc scan did not show a free intraperitoneal distribution, but a repeat scan was normal after pretreatment infusion of lactated Ringer's solution. The patient had previously had 3 laparotomies.

Clinical effect

Stable disease was seen in 4 of 8 evaluable patients. In 2 of the patients CT showed a stationary tumour volume after 2 and 4 cycles, respectively, and progression was demonstrated after a further 2 cycles. In another 2 patients the evidence of progressive disease was equivocal and the patients had an excellent performance status at the first treatment evaluation after 3 months. They were given 2 and 5 more cycles of therapy, respectively, before definite progression was demonstrated.

GENERAL DISCUSSION

I. LIVER RESECTION

Mortality and morbidity

Operative mortality rates in liver resection for hepatic tumour range from 0% to 20% (Table 2). Primary liver cancers carries a high operative risk because of presence of liver cirrhosis and/or alcohol abuse in some patients, with liver failure as a major cause of postoperative death (Iwatsuki et al 1983). Furthermore, reported results are influenced by the number of major resections and whether or not wedge resections are included.

The morbidity rates range from 13% to 46%. It is obvious that although operative mortality has decreased in recent reports from experienced centres, there is still a substantial risk of postoperative morbidity. The predominant complications in this study (I) and others (Iwatsuki et al 1983, Thompson et al 1983) were bleeding, infection and liver failure. Intraoperative bleeding, necrotic liver tissue or accumulation of bile may result in recurrent bleeding, abscess formation and/or sepsis. The liver resection may in itself lead to liver insufficiency, and this condition may, furthermore, be precipitated or aggravated by any of the above-mentioned complications.

Surgical technique

Extension of the abdominal incision into the thorax has been advocated as an essential step to provide adequate exposure (Pinkerton et al 1971, Donovan et al 1973). In 1982, Ryan et al reported that thoracic extension was associated with a significantly prolonged operation time, increased blood loss and increased morbidity. Our patients were operated with an abdominal incision only and adequate exposure was achieved.

There are two principal techniques in liver resection. Preresection ligation, consists of dissection and ligation of the portal pedicle and the hepatic vein of the liver lobe to be resected (Lortat-Jacob et al 1952, Quattlebaum 1953). This technique has two disadvantages: dissection of the hepatic vein is dangerous with a risk of tearing or penetrating the vein and causing massive bleeding; and there is a risk of erroneous ligation of hilar vessels (Bismuth 1982a).

The direct parenchymal, approach is the intrahepatic vascular access and was introduced by Ton That Tung in 1963. This technique may have the disadvantage of increased intraoperative bleeding (Bismuth 1982a). However, in the present study (I), increased bleeding was not observed. Ton

That Tung advocates simple clamping of the porta hepatis (maximum 10 min.) in major liver resections to reduce vascular inflow and bleeding. Bismuth (1982a) recommends a combination of the two techniques with dissection of the porta hepatis and clamping of the arterial and portal elements to the lobe to be resected, combined with intrahepatic access to the hepatic vein.

Previously, it was believed that clamping of the portal triad for more than ten minutes is harmful. This belief was based on findings in experimental animals. Raffucci & Wangenstein (1951) reported that hepatic inflow occlusion resulted in fatal splanchnic congestion, which could be avoided by simultaneous occlusion of the splanchnic inflow. Hepatic and splanchnic inflow occlusion in pigs for 15 minutes was found to induce lactic acidosis and was considered potentially harmful (Almersjö et al 1971). In patients, however, the liver tolerates prolonged normothermic ischemia unexpectedly well, as demonstrated by Huguet and associates (1978). The authors used either simple portal triad clamping for up to 20 min., or hepatic vascular exclusion (additional clamping of the inferior vena cava above and below the liver) for a maximum of 65 min. No adverse effects were encountered, except for metabolic acidosis secondary to splanchnic and/or lower limb stasis, and sodium bicarbonate was used to normalize arterial pH.

In conclusion, the direct parenchymal approach is preferable in routine performance of major liver resections. If technical problems are encountered or expected, simple clamping of the entire portal pedicle is possible, and the use of this approach should have no harmful consequences.

The technique of transecting the liver parenchyma may also influence the bleeding. The parenchyma is transected bluntly with hemostats, the suc, the back of a knife or with fingers ("finger fracture"; Lin et al 1960). Recent studies have suggested a new technical approach, the ultrasonic dissector, to be an effective instrument minimizing the (mechanical) bleeding (Hodgson & DelGuercio 1984, Tranberg et al 1986).

Bleeding

Following liver resection, coagulation factors of the prothrombine group (factors II, VII, X), factor V, factor IX, fibrinogen and plasminogen are markedly decreased (Nihlén et al 1966, Almersjö et al 1967, Coppa et al 1985). Presumably, transfusion of stored blood accounts for some of the decrease in the labile clotting factors (V and VIII).

In trauma patients, Miller et al (1971) demonstrated that a significant bleeding tendency occurred after transfusion of

20-25 units of stored blood and that all patients with platelet counts below 60,000 had a bleeding diathesis. Correction of clotting factor deficits with fresh frozen plasma did not reverse the state of bleeding. However, transfusion of 3-4 units of fresh blood increased the platelet counts and bleeding ceased. The authors concluded that a dilutional, quantitative defect in platelets was the cause of bleeding. In addition to clotting factor deficit and thrombocytopenia, a qualitative defect in platelets was demonstrated by Lim and coworkers (1973) in patients receiving multiple transfusions of blood.

In liver injury, nonmechanical haemorrhage is a major cause of death. Mortality was 41% in patients with bleeding diathesis and 0% in those without nonmechanical bleeding, as reported by Clagett and Olson (1978). The authors found, as we did (I), that reduction in platelet counts varied with the number of blood transfusions received. Consequently, the additional effects of liver resection and multiple transfusions of stored blood on the number and function of platelets, as well as on the coagulation factors, supports the notion that administration of fresh frozen plasma and platelet concentrates is an essential part in the intraoperative management of liver resection. The liberal and prophylactic use of blood components, especially platelet concentrates, may account for the absence of nonmechanical bleeding in the present study.

One of our patients died from bleeding duodenal ulcer during a postoperative course with subphrenic abscess and two reoperations (I). Acute gastroduodenal mucosal lesions or stress ulcers are not uncommon experience in major liver resection (Pinkerton et al 1971, Iwatsuki et al 1983) or in other major surgery. High risk patients in general surgery may benefit equally from cimetidine or antacid prophylaxis to prevent gastrointestinal bleeding (Basso et al 1979). In a randomized study of 52 patients subjected to liver resection, Nagasue et al (1984) demonstrated a significantly lower frequency of bleeding, 6%, in cimetidine treated patients (200 mg x 6 for a week after operation, or a month if postoperative complications were present) as compared to 28% in control patients. However, the authors also found a tendency toward more frequent liver failure and postoperative hepatitis in the cimetidine treated group. This finding may be clinically relevant, because cimetidine has been shown to induce significant suppression of liver regeneration after two-thirds liver resection in the rat (Kanashima et al 1983). The conclusion, therefore, is that antacid prophylaxis is preferable to cimetidine for routine use and should be given to all patients with a complicated postoperative course.

Infection

Postoperative infection is one of the most frequent complications following liver resection. The main preventive measures include intraoperative hemostasis and avoidance of leaving ischemic liver tissue at the resection margin, that is tissue devitalized by preresection ligation or deep mattress sutures.

Most surgeons use prophylactic antibiotics in liver resection. In a study of 8 patients resected because of liver injury, Vajrabukka and colleagues (1975) found 22 sites of infection, but in only 2 cases were the first isolated organisms sensitive to the prophylactic antibiotics given. The only patient who did not develop any clinical infection was the only patient not given any prophylaxis. Drains and catheters often harboured bacteria, and infection of T-tube bile was always accompanied by other infections, such as subphrenic abscess, peritonitis or empyema. In the present study (I), all patients with postoperative infections had received prophylactic treatment.

In elective liver surgery the routine use of prophylactic antibiotics should be questioned. However, in liver resections associated with biliary obstruction (Tanaka 1984), bile duct resection, bilio-enteric anastomosis (or gastro-intestinal resections), administration of prophylactic antibiotics may be preferred and should be adjusted according to the results of intra- and postoperative cultures.

Laboratory values

In experimental animals subjected to liver resection, alkaline phosphatases (ALP) has been found to increase in liver and serum (Aronsen et al 1970). The clinical experience is variable and various authors have reported a transient decrease (Aronsen et al 1969), no change (Almersjö et al 1969a) and an increase (Pack & Molander 1960). Our findings (I) may explain the discrepancy. Patients in whom serum ALP was elevated because of liver cancer had a pronounced decrease after resection, whereas patients with little or no elevation in ALP showed only minor postoperative changes. Thus the increase in ALP caused by the resection itself is often outweighed by the decrease caused by the removal of the cancer.

Variation in ALP seems to depend more on the kind of tissue removed and less on the degree of damage to the liver cells. This is in contrast to the behaviour of other liver enzymes (Bengmark & Tranberg 1985). Transferases and also bilirubin increased in proportion to the amount of liver resected, as demonstrated in the present study (I).

Following major liver resection, the bilirubin level peaks during the first postoperative week and should normalize within the next week or two, as shown by us (I) and others (Pack & Molander 1960, Stone et al 1969, Aronsen et al 1969). If bilirubin deviates from this pattern, the possible causes are numerous and demand a detailed etiological investigation. It is important to demonstrate abscess or biliary duct obstruction because these should be corrected surgically. However, it is equally important to demonstrate hepatocellular damage in order to avoid an unnecessary and potentially harmful reoperation. In our series, misinterpretation of the significance of the elevation of bilirubin, led to a negative exploration for intra-abdominal abscess in 2 patients.

Metabolic disorders

The rationale for plasmapheresis in liver failure is the removal of potential toxins that might be cytotoxic for the hepatocytes and disturb the regenerative capacity of the liver cells, ammonia being particularly relevant (Hughes et al 1976, Ellis et al 1979). To date, the experience of this kind of treatment in postoperative liver failure is limited. Preventive measures include estimation of the remnant hepatic capacity and minimizing the resected liver volume. A method of prediction using imaging and functional analysis was recently described by Yamanaka and associates (1984). When hepatic lobectomy is expected to reduce the liver function below the risk limit, the authors advocate wedge resection, if possible, instead of major resection. Minor anatomical liver resection, such as bisegmentectomy and segmentectomy, is an alternative to atypical local excision and the technique is described in detail by Ton That Tung (1979) and Bismuth et al (1982b).

Major hepatic resection may impair the ability of the liver to maintain the concentration of glucose in the blood. This is due to removal of liver parenchyma and thus liver glycogen, together with the decreased absolute capacity for gluconeogenesis and a surgically induced depletion of glycogen in the remaining liver. The risk of hypoglycemic problems is inversely proportional to the amount of remaining normal parenchyma, and can generally be counteracted by giving hypocaloric glucose solutions for the first postoperative days (McDermott et al 1963, Stone et al 1969). However, hypoglycemia may still occur (Vajrabukka et al 1975). The fact that we did not experience any episodes of hypoglycemia in our patients is attributed to our policy of filling the glycogen stores preoperatively by glucose infusion.

Many authors have recommended intravenous albumin supplements during the postoperative period (McDermott et al 1963, Aronsen et al 1969, Almersjö et al 1969b, Stone et al 1969, Donovan et al 1973). The rationale is to counteract the rapid decrease in serum albumin seen after liver resection. Albumin is produced in the liver only, and contributes to the colloid osmotic pressure of the plasma. A decreased synthesis cannot, however, be the sole explanation for the rapid and considerable decrease in serum albumin, considering that the half-life of albumin is about 17 days (Bauman et al 1955). Other factors such as loss of blood and plasma, dilution, leakage of protein from the raw liver surface, and transcapillary leakage are probably more important than the reduction in synthesis.

We have deleted albumin from the routine postoperative regimen and this did not appear to have any adverse effects in our patients (I). A similar attitude was reported by Vajrabukka and colleagues (1975). Administration of albumin (and plasma) might be considered when the albumin level is so low that the patient is at risk of developing interstitial edema due to the decrease in plasma oncotic pressure. However, Grundmann and Heistermann (1985) could not verify the benefits of this substitutional therapy in a prospective study of ICU patients with a low (<24 cm water) colloid osmotic pressure in plasma.

Determinants of survival and recurrence

In patients not treated by liver resection, Goslin and associates (1982) reported a significant difference in survival for patients with 1, 2 or 3 metastases, as compared to those with 4 or more. There does not seem to be any specific reason for choosing the number 4, but by doing so, we could demonstrate that this applied also to patients subjected to liver resection (II). Previously, August et al (1985a) and Cady & McDermott (1985) have reported similar findings in univariate analyses. In our study, the 3- and 5-year survival rates after resection of single metastases were 45% and 24%, respectively. For patients with less than 4 tumours, the figures were similar, 41% and 20%. This strongly supports the view that not only patients with single metastases, but also those with 2 or 3 tumours should be resected.

The favourable prognosis for patients with less than 4 liver tumours may be explained by a different biological behaviour of the metastatic disease in some of these patients. Tumour cell emboli from the colorectal cancer enter the liver via the portal vein (Willis 1973). The liver tissue is highly favourable for tumour growth and there is a high incidence of "takes" from embolic cells. Decreased capacity of the primary tumour to release emboli with sufficient number of

vital cells or increased inhibitory influence of the host organ may account for the limited number of liver deposits in some patients (Warren 1982).

Next generation, tertiary, hepatic metastases occur frequently in liver tumours (Willis 1973). By contiguous tumour growth from the first liver metastasis, the portal vein or any of its branches may be invaded and tumour emboli are formed. The size of the invaded vein is important, because emboli from a large central branch may result in a wide dissemination, whereas invasion of a small peripheral venule may be the origin of new metastases that are close satellites to the parent tumour. In our study, 10 patients had "solitary" metastases with satellites, and their median survival and time to recurrence was significantly shorter than in patients with a "truly" solitary metastasis. Consequently, some cases of multiple metastases could be considered as single tumours of a later stage and with a worse prognosis when satellites within the same liver segment were found at operation or evidenced preoperatively.

It would seem natural to consider the disease generalized and consequently unresectable if there are bilateral liver tumours. This is a common view (Foster & Lundy 1981) and accounts for the limited experience from resection in patients with bilateral disease. In some centres, however, bilateral wedge resections or lobectomy combined with contralateral wedge resection are sometimes performed. In 1985 Augustal and colleagues reported significantly shorter survival in patients with bilateral as compared to unilateral metastases. Recently, Butler et al (1986) reported survival rates without significant difference for patients with disease in one or two liver lobes. We found, that although the risk of early recurrence was moderately increased in bilateral as compared to unilateral disease (III), survival was not significantly shorter (II). Consequently, the chance remains that patients with bilateral tumours will benefit by liver resection.

Regarding the number and size (more or less than 4 cm) of liver tumours, Adson and associates (1984) observed that resection of multiple small metastases did not improve survival. Resection of single tumours, large or small, had a good prognosis. Unexpectedly, patients with large multiple lesions also had a favourable survival. In our study (II), we could verify a significant difference between single and multiple small tumours, whereas the prognosis for large tumours, single or multiple, was similar. The point to remember is that when several small metastases are seen there are probably many more that are hidden, whereas in cases with a few large tumours (less than 4) the disease may still be localized, and a large size of tumour does not

always imply an advanced disease.

The percent of tumour volume in the liver measured at preoperative angiography or laparotomy has been shown to influence prognosis in untreated patients (Bengtsson et al 1981) and in patients given regional chemotherapy (IV). Recently, Gennari et al (1986) demonstrated survival differences after liver resection for patients with stages I-III, which were classified by means of differences in liver tumour volume. However, also included in the staging system were such variables as single or multiple metastases, unilateral or bilateral spread and presence or absence of extrahepatic disease. Influence on survival by liver tumour volume in itself was not demonstrated.

In our study (II, III), the risk of early recurrence was increased, but the frequency of recurrence was similar in patients with varying amounts of tumour (more or less than 25% hepatic replacement). The liver tumour volume had no independent impact on survival in the multivariate analysis. However, none of the 5 patients with a tumour volume exceeding 50% lived for 3 years. These prognostic results should, in my view, influence the surgeon to not resect a patient with more than half the liver replaced by tumour.

Extrahepatic disease is generally considered as contraindicating liver resection. A few reports (Fortner et al 1984a, Adson et al 1984) have included patients with extrahepatic metastases, resected when the liver metastases were resected, and the patient survival was short. In our series, the major impact of extrahepatic metastases on survival and risk of early recurrence was demonstrated (II, III). It should be emphasized that even if excluding patients with preoperatively demonstrable extrahepatic disease, regional spread to the lymph nodes in the porta hepatis should be ruled out before liver resection by lymph node biopsy and rapid morphology. Lymphatic metastases in the hepatic region are most certainly derived from the liver tumours and these remetastases signify a generalized spread (August et al 1985b).

Type of operation (lobectomy, segmentectomy or wedge resection) did not influence survival significantly according to Petrelli et al (1985). Logan and coworkers (1982) observed different mean survival after trisegmentectomy (11 months), lobectomy (24 months) and wedge resection (45 months) with 6 to 8 patients in each group. Comparing wedge resection with major resection, we could demonstrate no difference in survival (II). However, the risk of early recurrence and the frequency of relapse in the liver was increased for patients subjected to major liver resection (III). These results may be due to nontreatment factors underlying the surgeon's choice of

resection type, but the differences could also be interpreted as an independent influence of the type of resection. It has been reported that prolonged anaesthesia and major surgical procedures act as immunosuppressors (Lundy 1980). A postoperatively altered host-tumour relationship may be a mechanism by which remnant cancer cells escape immune destruction. Consequently, when there is a choice of surgical procedures that would excise all visible tumour, a minor resection is preferable. Differences in recurrence after major and wedge resections should be taken into consideration in protocols for adjuvant treatment after liver resection.

It was not unexpected, to find as we did, that a nonradical resection with tumour in the resection margin was followed by early recurrence and short survival (II, III). But, for how wide a margin should the surgeon aim? The recommendation by Foster & Lundy (1981), that 1 cm margin suffices, was substantiated by our results: less than 10 mm margin of resection influenced prognosis negatively. Consequently, a 1-cm tumour-free margin should be sought, also in wedge resections. Considering the tendency of the tumour to spread by microemboli in the parenchymal venules close to, but outside, the visible hepatic deposit, even a wider margin of resection might be beneficial. This was suggested by Rajpal and coworkers (1982), who demonstrated a significant difference in survival after major liver resection, separating the patients at a limit of 20 mm resection margin.

Indications for liver resection

Determinants of survival and recurrence should be considered when indications for liver resection are formulated. In summary, patients with less than 4 liver tumours, no extrahepatic metastases (including liver hilum lymph node deposits), and an estimated tumour volume less than 50% of the liver may be subjected to liver resection. Bilaterality or suspected satellites to a solitary tumour are negative signs, but should not contraindicate resection. A resection margin of more than 10 mm should always be attempted, and if not expected possible to achieve, the tumour should be considered unresectable.

In a recent communication by Cady & McDermott (1985), the timing of liver resection was discussed. The authors argued that truly solitary, double or triple liver metastases will remain as such and therefore a "test of time" after discovery was suggested. This method of selecting biologically suitable candidates would, according to the authors, after a period of 2 to 6 months reveal the patient's true nature of disease. I do not agree for two reasons. First, patients with the most favourable prognosis

are those with a small single metastasis (5-year survival 40%). Second, with time, the development of next generation metastases will potentially worsen the prognosis.

Sites of recurrence

It was clearly demonstrated in this study (III), that intra-abdominal recurrence was the major site of failure in patients subjected to resection of colorectal metastases. Three quarters of the patients had relapse in the abdomen, and this occurred in 94% of the patients with recurrence. In previous reports (Table 5), the risk of hepatic recurrence after liver resection in 168 patients was much less compared to our findings (34% and 65%, respectively), but the risk of extrahepatic relapse was similar (40% and 50%). Analysis of 99 patients with relapse (Table 5) and comparison with our results (III), revealed a similar proportion of patients with recurrence in the liver-only (31% and 36%), and similar proportions of extrahepatic relapse (69% and 64%). However, in the present study, hepatic recurrence (with or without relapse at other sites) was relatively more common (83%), and accordingly the proportion of patients with extrahepatic relapse alone was lower (17%).

In our study, the increased risk and proportion of hepatic recurrence may be explained by two main factors. First, our policy to operate on patients with relatively advanced disease: the frequency of 4 or more tumours were not stated, but multiple liver metastases present in about 30% of the patients in the previous reports as compared to 50% in our material. In most reports, presence or absence of extrahepatic metastases was not commented upon. Second, a clinical material always underestimates the frequency of recurrence in the liver (and also in the peritoneal cavity). Lower frequencies were noted in clinical as compared to necropsy series by Gilbert et al (1984); to a large extent because of less accurate clinical assessment. Laparotomy, which was performed in one third of our patients, decreased the risk of underestimating intra-abdominal recurrence at the time of initial relapse. The frequency of laparotomy in previous reports (Table 5) was not stated.

A dominance of intra-abdominal recurrence is similarly found after resection of primary colorectal resection (Table 4). Liver recurrence is, however, less frequent after the primary resection as compared to the liver resection. The fact that a liver resection material represents a selected group of patients with established liver disease apparently accounts for this difference.

Half of the patients with relapse after colorectal resection has recurrence at the resection site. This is a most notable frequency with implications for patients subjected to liver

resection. In our material, 15% of patients with relapse had recurrence at the colorectal resection site and although comparatively low, this frequency was unacceptably high. A substantial part (20-45%) of local failures occur more than 2 years after bowel resection (Cass et al 1976, Rao et al 1981). Consequently, patients with a few years interval between bowel and liver resection also carry a risk of local recurrence. This implies that investigations to reveal local relapse should be performed before liver resection as well as during follow-up.

Time to recurrence

O'Connell and associates (1985) reported a median (actuarial) time to progression of 24 months, and Fortner et al (1984a) reported an interval to relapse of about 20 months. Butler et al (1986) demonstrated a median disease-free interval of 15 months in patients with relapse, and in our material (III), the period was 9 months. Fortner and coworkers (1984a) reported that 94% of the recurrences occurred within 2 years, including all patients with relapse in the liver or the lungs, and only one recurrence (in bone) was encountered more than 2 years after hepatic resection. O'Connell et al (1985) observed the last patient relapse 2.5 years after resection, and in our patients it occurred 3 years after operation.

When planning follow-up or adjuvant treatment after resection of colorectal liver metastases, these data should be considered. Investigations concentrated during the first 2 years would be expected to find most recurrences and patients disease-free more than 3 years after liver resection may have a substantial hope for cure.

Benefit of resection

The selection of patients for liver resection can be evaluated in terms of survival and time to relapse, but also in terms of the proportion of patients who benefited by surgery. Adson & van Heerden (1980) analysed 32 patients on an individual basis in terms of symptoms, recurrence and survival, and concluded that at least 20% and perhaps 30% of their patients benefited by major hepatic resection.

Operative mortality and patients dead within a year are obvious failures. Success is more difficult to assess, and I have chosen to make two classifications of probable and certain success. The overall 5-year survival was 16%, which was the ratio of certain success. Probably successful cases included all patients with a disease-free interval after liver resection exceeding 2 years, which was 25%.

Our present indications for liver resection should be modified. The guidelines given above may identify patients most likely to benefit from resection. It is recommended, that exclusion criteria for liver resection includes: 4 or more tumours, extrahepatic metastases, more than 50% hepatic replacement by tumour and lesions unaccessible for resection with 10 mm margin. It should be noted, that 3-year and 5-year survival rates for patients with any of these criteria were less than the corresponding survival rates after hepatic arterial infusion of 5-FU (10% and 5%, respectively).

The moderate ratio of patients who benefit by liver resection implies that an effective adjuvant treatment after surgery is necessary. Intra-arterial and intraperitoneal chemotherapy as adjuvant treatment is discussed below.

II. REGIONAL CHEMOTHERAPY

Survival and response

The overall median survival of 11 months after HAI chemotherapy (IV) was in agreement with previous reports (Table 6). In the literature, criteria for response are inconsistent. A one-third reduction in serum levels of carcinoembryonic antigen (CEA) was the sole evidence of improvement demanded by Balch et al (1983). Reduction in liver size at abdominal palpation was regarded as a sign of response by Ansfield et al (1975). Partial remission was defined by Patt et al (1983) and Weiss et al (1983) as a greater than 50% reduction of the sum of the products of two perpendicular diameters of the liver tumour, evaluated by an imaging method. Abdominal palpation or imaging techniques were used by Petrek et al (1979), Reed et al (1981) and Daly et al (1985). We defined partial response as a decrease, of unspecified extent, of the tumour volume with a duration of at least 3 months. The response rate (36%) in our study was in agreement with those reported (29-43%) by Weiss et al (1983) and Patt et al (1983). Higher response rates were encountered, when less rigid criteria were used.

Many authors compare survival for responders with survival for nonresponders, implying that the statistically significant difference, which is most often found, proves the efficiency of the treatment. Nonresponders are regarded as a "control" group, and their survival is assumed to be equivalent to the survival of untreated and unselected patients (Cady & Oberfield 1974). This substitute for a controlled clinical trial is apt to be misleading. Statistical comparison of survival by response is biased, mainly because patients who die before the first response evaluation are automatically referred to the nonresponders (Anderson et al 1983). Furthermore, correlation is not the

same as cause. It is not possible to provide evidence in a clinical trial that response causes longer survival (Anderson et al 1983). Probably, there is a biological difference between tumours of responding and nonresponding patients, and responding tumours may constitute a favourable subgroup regardless of treatment. Goslin et al (1982) reported that patients with response had no bad prognostic factors at presentation and their survival of 18 to 24 months would have been predicted regardless of treatment.

If there is a survival difference between responders and nonresponders, the response criteria may be used for prognostic evaluation during therapy and in the decision on whether treatment should be discontinued or not. In our study (IV), partial response/stationary disease was associated with a good prognosis and nonresponders carried a high relative risk for a short survival, the impact of other prognostic factors taken into account. This implies that our criteria for response could be used for prognostic evaluation during treatment, but there is no implication on the benefit of the treatment.

Clinical effects of intraperitoneal chemotherapy in established colorectal liver cancer has not been evaluated previously. Stationary tumour volume was seen in half of the evaluable patients in the present study (V), and these data suggest that the clinical effects of IP infusion are comparable to those of HAI chemotherapy.

Considering the palliative role of regional chemotherapy, patients for HAI or IP treatment should be selected only among those with nonresectable liver metastases. Patients selected for regional chemotherapy by Balch and colleagues (1983), had less than 4 liver tumours in 46%, solitary liver deposits in 15% and unilateral distribution of disease in 35%. Statements on possible resectability were not made. On the other hand, patients should not be included when extrahepatic metastases are considerable or a poor performance status suggests decreased tolerance to treatment. Johnsson et al (1985) did not exclude patients with jaundice or ascites, and these factors were not unexpectedly found to aggravate the prognosis.

Determinants of survival

In the only previous multivariate analysis of prognostic factors after HAI chemotherapy in colorectal liver disease, Fortner et al (1984b) found, as we did (IV), a dominance of nontreatment factors. In both studies, the extent of hepatic replacement by tumour and presence or absence of lymph node metastases in the hepatic region were variables that governed prognosis. In previous studies, using single-variable analyses, the prognostic influence of liver

tumour volume was demonstrated by Cady & Oberfield (1974), Daly et al (1985) and Johnsson et al (1985), whereas tumour volume impact was less pronounced in the study by Balch et al (1983). Presence of extrahepatic disease had no impact on survival according to Cady & Oberfield (1974), but later reports did not agree (Niederhuber et al 1984, Johnsson et al 1985).

In the literature, there is no consistent difference in prognosis for patients with liver metastases found at the time of diagnosis of colorectal cancer compared with patients who have a disease-free interval (Oberfield et al 1979, Goslin et al 1982). We did not find any difference comparing survival curves for patients with synchronous or metachronous disease. However, in the multiple regression analysis, the disease-free interval was proportional to length of survival (IV). It has been shown that some prognostic influence is associated with liver function tests, such as the transferases (Cady & Oberfield 1974, Fortner et al 1984b). The negative influence of bilirubin and alkaline phosphatases in our study was recently confirmed by Johnsson et al (1985).

In contrast to a previous report by Kim et al (1977), the present study could not demonstrate any survival influence of hepatic tumour vascularity, as seen at angiography. Our results were supported by the findings of Daly et al (1985), who reported that response to HAI chemotherapy did not vary with tumour vascularity as shown by arteriogram. However, the authors found a significant predictive value of the degree of vascularity, as estimated by 99mTc-macroaggregated albumin arterial flow scan. Consequently, a prognostic influence of tumour vascularity cannot be excluded, and further studies should confirm its role.

In this study (IV), we could not demonstrate whether HAI chemotherapy was beneficial to the patients or not. However, using multivariate analysis, the most important nontreatment factors could be controlled and varying treatment approaches could be compared. It was found that prolonged infusion was superior to pulse administration of 5-FU. This is important considering that the effect of treatment probably is marginal, and therefore the "best" approach should be selected for prospective trials. Temporary dearterialisation was accompanied by a decreased survival as compared to regional infusion alone. This was in apparent contrast to the finding that hepatic artery thrombosis varied positively with survival. Influence of hepatic artery thrombosis on survival has been demonstrated previously in a study by Oberfield et al (1979), and in a preliminary report by Patt et al (1981). It is conceivable that a comparatively high drug concentration leads to damage of the vessel walls and thrombosis formation. Conversely, the mechanism may be that

partial thrombosis reduces the blood flow with a consequent increase in the arterial drug concentration (Ensminger & Gyves 1985). It remains to be demonstrated, that intentional occlusion, intermittent and partial, prolongs survival for patients on HAI chemotherapy. An implantable device for intermittent occlusion has been developed (Persson et al 1984), and studies on its clinical use are in progress.

It should be noted that liver hilum lymph node metastases influenced the survival in both regional chemotherapy (IV) and in resective treatment (II). This emphasizes the need for abdominal exploration and quantification of hepatic and extrahepatic disease. Surgical catheter placement also allows for ligation of aberrant hepatic arteries or the right gastric artery. This may increase treatment efficacy and decrease gastroduodenal chemotoxicity (Barone 1984). It has been suggested that duration of survival is longer with surgical than with percutaneous placement of the catheter. However, differences are not impressive and may be explained by selection of patients. Regardless of whether the catheter is placed percutaneously or surgically, the perfusion pattern should be assessed with scintigraphy to verify perfusion of the entire liver (Kaplan et al 1978, Yang et al 1982).

To summarize, in a clinical trial for regional chemotherapy the benefit of long-term infusion versus no treatment should be tested. Stratification for liver tumour volume, liver hilum lymph node metastases, and synchronous/metachronous disease is recommended.

Complications

Complications in HAI chemotherapy are mainly associated with the operative procedure, the intra-arterial access device, or chemotherapy toxicity. In patients treated with 5-FU infusion via a percutaneously placed catheter, complications related to the catheter predominate, i.e. catheter dislodgement, sepsis, arterial aneurysm or thrombosis (Goldman et al 1974, Petrek et al 1979). The use of peroperatively placed catheters reduces the risk of catheter dislodgement, but the operative trauma induces an additional risk. In a study on 88 patients with colorectal liver metastases, Reed and coworkers (1981) found 12% operative mortality, and causes of death included abdominal abscess, tumour necrosis, portal hypertension, perforated gastric ulcer and drug toxicity. The authors argued that some complications occurred because therapy was effective in patients with massive hepatic replacement. Inclusion of high risk patients was reasoned by Cady & Oberfield (1974) to account for 6% operative deaths in liver failure.

With the introduction of a totally implantable pump and a silicone rubber catheter by Blackshear et al (1972), the occurrence of catheter cracking or leakage, catheter sepsis, and hepatic artery thrombosis was reduced or absent (Balch et al 1983, Cohen et al 1983, Weiss et al 1983). Although pump malfunction and catheter-related complications during treatment are rare in series with implantable devices, morbidity is not negligible. It was 10% in a recent study by Daly et al (1984), and included arterial thrombosis and pump pocket infection.

The rationale of regional chemotherapy is a high tumour concentration of the drug combined with a low systemic concentration. Recent data indicate that systemic toxicity is replaced in HAI chemotherapy by regional toxicity, including gastritis, gastroduodenal ulcer, acalculous cholecystitis, chemical hepatitis and bile duct strictures. Daly et al (1984) reported 48% gastroduodenal inflammation including 30% endoscopically verified ulcer, 65% hepatitis and 5% bile duct strictures. The experience of Johnsson et al (1985) was even more discouraging with 3 deaths due to ulcer disease, 2 from bile duct strictures and 1 from chemical hepatitis among 40 patients.

In the present study (IV), 30% of the patients had gastrointestinal morbidity whereas no unequivocal hepatitis was encountered. These results are in accordance with those of Schwartz and coworkers (1985), who reported gastrointestinal complaints in 53% and jaundice in 20% of the patients. The varying frequency of toxicity is difficult to explain, because almost identical drug schedules (FUDR 0.3 mg/kg/d for 2 weeks every month) have been used by the above-mentioned authors (Daly et al 1984, Johnsson et al 1985, Schwartz et al 1985). Regional chemotoxicity may be decreased by dose reduction, cholecystectomy and by measures preventing catheter dislodgement or spill-over of the infused drug to arteries of the gastric and duodenal area (Narsete et al 1977, Chuang et al 1981, Barone 1984). However, Kemeny et al (1984b) observed no beneficial effects by ligating arteries supplying the stomach and duodenum, and therefore suggested, that FUDR or its metabolites were ulcerogenic causing duodenal ulcer after excretion into the bile.

In an early treatment approach, ligation of the hepatic artery was used. Ischemia and central necrosis of the liver tumours were achieved (Sparks et al 1975). However, the postoperative mortality was high, 16% to 40% as reported by Almersjö et al (1976) and Koudahl et al (1972). This was confirmed in a recent study by Didolkar and colleagues (1985) on 30 patients treated with hepatic dearterialisation and HAI chemotherapy because of colorectal liver metastases. Mortality not related to the malignancy was 20%, and causes

of death included multiple liver abscesses and bleeding peptic ulcer. The experience of high morbidity rate and the finding that collaterals to the liver develop shortly after hepatic artery ligation (Bengmark & Rosengren 1970) led to the introduction of temporary dearterialisation (Bengmark & Fredlund 1974, Dahl et al 1981). In the present study (IV), however, morbidity and mortality was increased in the patients undergoing temporary dearterialisation, and abscess formation was one of the main causes.

The surgical trauma in intraperitoneal chemotherapy is minimal, and operative mortality zero. Most authors have used a technique originally developed for home peritoneal dialysis in chronic renal failure (Jenkins et al 1982). A Tenckhoff catheter for IP access is placed at the level of the umbilicus under local anaesthesia. Instillation and drainage of fluid containing the drug or repeated bolus infusions are subsequently performed (Myers & Collins 1983). Complications related to the use of the percutaneous catheter are relatively frequent. Jenkins and coworkers (1982) reported intestinal perforation at catheter implantation in 4% of 78 patients, infection related to the catheter in 8%, and leakage of fluid around the catheter, intermittent inflow obstruction or failure to drain in nearly every patient. Myers & Collins (1983) reported bacterial peritonitis and pain, irritation and abdominal discomfort in 21% of the patients. Kaplan et al (1985) had 32 episodes of infectious peritonitis in the treatment of 90 patients. August and associates (1985a) discontinued therapy because of bacterial peritonitis in 1 and abdominal pain or nausea in 3 of 21 patients.

Apparently, the use of an implantable device for IP access reduces infectious complications and increases patient acceptance. Like us (V), Gyves and coworkers (1984) used a subcutaneous portal and had no intra-abdominal infections. The risk of portal pocket infection remains, but should be minimal, as shown in recent reports on the use of implantable portal for HAI chemotherapy (Balch et al 1983).

Sugarbaker and colleagues (1985) reported significantly less hematologic toxicity (leucocytopenia) after IP (15%) than IV (57%) infusion of 5-FU in a randomized trial. The incidence of elevated transferases was about 60% and similar in the two groups. The dose-limiting toxicity in IP chemotherapy is not assured, but probably it is regional (Gyves et al 1984, V), as evidenced by common occurrence of chemical peritonitis or mild abdominal discomfort. The use of TcSc scan (Tully et al 1973) or CT (Dunnick 1979) before onset of chemotherapy to ensure uniform IP distribution should be emphasized. Localized chemical peritonitis may occur if distribution of the drug solution is restricted.

Pharmacokinetics of IP infusion

Drugs administered into the abdominal cavity pass over the peritoneal surface by diffusion either through the parietal or the visceral peritoneal surface or by absorption via the lymphatic drainage. Drugs can pass the peritoneum via intracellular pores or transcellularly. The latter depends on lipid solubility, whereas intracellular passage depends on the molecular size of the drug. The rate of drug absorption is determined by the surface area exposed to the drug and by the permeability of peritoneum. The permeability area product (PA; ml/min) is roughly inversely proportional to the square root of the molecular weight (Dedrick et al 1978, Myers & Collins 1983). The regional advantage in IP chemotherapy is derived from relating the IP 5-FU concentration (C) to the 5-FU level in the systemic circulation, and may be calculated by the formula (Speyer et al 1980):

$$\frac{C \text{ intraperitoneal}}{\text{-----}} = \frac{\text{TBC}}{\text{PA}} + 1$$

C plasma

Using an estimated PA of 14 ml/min (Gyves et al 1984) or 21 ml/min (Speyer et al 1981), it was calculated from data of the present study that the mean intraperitoneal level of 5-FU was 476 or 714 times higher than the systemic concentration. This agreed well with estimations by Speyer et al (1980) who found a mean ratio of 298 (range 111-898). Gyves et al (1984) reported generally lower systemic levels and, accordingly, a higher ratio (2,559).

After passage of the visceral peritoneum, the drug will drain into the underlying capillaries and the portal circulation. It has been estimated that most (about 80%) of the intracavitary fluid is absorbed via the portal vein (Lukas et al 1971). Mainly because of uncertainty of portal vein flow and gastrointestinal tract metabolism, Speyer and colleagues (1981) could only estimate the proportion of 5-FU absorbed through the portal system to be in the range of 29-100%. The mean portal vein 5-FU concentration was 21 μM and the mean arterial level of 5-FU was 8 μM after 4 h dwell time exchange dialysis of fluid containing 1,040 mg 5-FU. These concentrations compared well with the estimated 5-FU levels in the hepatic artery (12 μM) and in the portal vein (1 μM) after intra-arterial 5-FU infusion of 10 mg/kg/d. A large proportion of the drug remains in the liver (first-pass effect) and hepatic vein concentrations have been shown to be about four times lower than portal vein levels (Speyer et al 1981).

The apparent total body clearance (TBC) in the present study (V) was 10 l/min, which is within the range reported by

others (3.7 - 18.4; Speyer et al 1981, Gyves et al 1984). This estimation is the overall net sum of complex pharmacokinetic events in multiple physiologic compartments (Collins et al 1980). When TBC exceeds the cardiac output (5 l/min), other organs such as the lung may have a substantial intrinsic clearance. Blood was believed to have no 5-FU clearance (Collins et al 1980). However, in the present study, a small but significant 5-FU clearance in whole blood was demonstrated. In practice, this is relevant, primarily for the handling of blood samples taken for 5-FU measurement.

In summary, the pharmacokinetic rationale for intra-peritoneal 5-FU infusion includes: a) high drug concentration on the peritoneal surface with potential effects on intra-abdominal disease; b) high portal vein concentration that may be important in an adjuvant setting for colorectal cancer, which seeds to the liver through the portal system; c) intrahepatic drug concentration comparable to the level achieved by hepatic arterial infusion; d) low systemic concentration of the drug infused.

Adjuvant treatment after liver resection

About 80% of the patients subjected to liver resection of colorectal metastases eventually succumb to recurrent disease, and it is obvious that additional treatment in an adjuvant setting is needed. The possible benefit of such treatment has not been evaluated in a controlled clinical trial. Some guidelines for the design of an adjuvant treatment protocol may be found in the present study (II-V).

Considering survival data (II), criteria for liver resection and adjuvant treatment should be: less than 4 liver tumours, absence of extrahepatic metastases, and a tumour volume not exceeding 50% of the liver. Patients with no tumour-free margin of resection should be excluded.

It is difficult to control for extrahepatic relapse, because no predictive factors could be demonstrated (III). The risk of hepatic recurrence may be partly controlled by stratification for the type of operation (major resection vs wedge resection), margin of resection (<10 mm vs > 10 mm), and intrahepatic distribution (unilateral vs Bilateral disease).

Following liver resection, intra-abdominal relapse occurs in nearly all patients with recurrent disease (III). This is important for the choice of drug administration. Survival benefit after HAI chemotherapy remains to be demonstrated, and even after technical advance, the morbidity cannot be neglected. The surgical trauma of catheter implantation

added to that of liver resection can be expected to increase the operative risk. Fortner and associates (1984a) reported a postoperative death because of portal thrombosis in a patient receiving intrahepatic adjuvant treatment after liver resection, and the authors have since abandoned this approach. In contrast, IP chemotherapy with an implantable device adds a minimal operative trauma, is easy to manage, achieves high concentration of drug intraperitoneally and drug levels in the liver comparable to those of HAI chemotherapy.

Until more efficient drugs are developed or superiority of drug combinations are demonstrated, 5-FU remains the drug of choice. Considering the better outcome for patients after prolonged infusion as compared to pulse administration in HAI chemotherapy, long-term treatment should be preferable also in IP therapy.

In order to prove a worth-while difference in survival between treated and control patients, a substantial number of patients is required. For instance, it is necessary to have 60 patients in each group to demonstrate, or exclude, an increase in (3-year) survival from 25% to 50%.

III. FUTURE ASPECTS

Bleeding, infection and liver insufficiency are the most frequent causes of postoperative morbidity following major liver resection. Technical advancements including the ultrasonic dissector and the YAG-laser should facilitate hemostasis and thereby also reduce the risk of infection. Since postoperative morbidity is more common following extended hepatic lobectomy, especially right lobectomies, modification of aggressive liver surgery may reduce the frequency of complications. When the hepatic functional reserve is small or resection is extensive, plasmapheresis or new drugs enhancing liver regeneration may prevent the occurrence of overt liver failure.

With better identification of patients likely to benefit from liver resection of colorectal liver metastases, survival rates may improve. However, recurrent disease can still be expected in a majority of the patients subjected to liver resection, and controlled clinical trials of adjuvant treatment are warranted. Intraperitoneal administration of 5-FU is recommended.

The great majority of patients with colorectal liver cancer have a nonresectable disease. Benefit from intrahepatic therapy has not been documented, but prospective randomized trials of HAI chemotherapy versus IV treatment are in progress. A two-armed trial with untreated patients would be preferable. Likewise, the benefit of IP chemotherapy in

established colorectal liver disease remains to be documented in a controlled trial. At present, chemotherapy for metastatic colorectal cancer should be given only in conjunction with clinical trials.

Combined treatment modalities are likely to improve treatment results. Hyperthermia or infusion of microspheres (with or without cytostatics or radioactive isotopes) might prove to be beneficial. Technical achievements related to induction of hepatic ischemia may reduce the morbidity previously connected to this approach.

SUMMARY

Complications and metabolic changes induced by major liver resection were analysed retrospectively. Major complications included bleeding, infection and liver insufficiency. The direct parenchymal approach was the favoured surgical technique. Nonmechanical bleeding was prevented by liberal transfusion of fresh frozen plasma and platelet concentrates. Routine use of prophylactic antibiotics was of doubtful value. Generally, the disturbances in metabolism associated with liver resection did not cause any problems. There was no need for routine parenteral nutrition or albumin administration. Preoperative infusion of glucose was probably responsible for the absence of hypoglycemia.

The 5-year survival rate after hepatic resection for colorectal liver cancer was about 20%. To improve evaluation of candidates for liver resection, the pattern of recurrence and the factors influencing survival were studied. It was demonstrated that early hepatic recurrence and short survival occurred in patients with 4 or more liver tumours, extrahepatic disease, and absence of a tumour-free resection margin. Liver tumour volume exceeding 50% was associated with a poor prognosis and no 3-year survivors.

Bilateral as compared to unilateral liver metastases did not have a demonstrable survival influence. However, the risk of early hepatic recurrence was increased. Likewise, patients subjected to major resection had an increased risk of hepatic relapse, as compared to those operated with wedge resection. No factor presently available was of any help in predicting extrahepatic recurrence. Three quarters of the patients had intra-abdominal relapse, which occurred in nearly all patients with recurrent disease after liver resection. This implies the need for adjuvant treatment and the findings should influence the choice of therapy.

In patients with nonresectable colorectal liver cancer, the 5-year survival rate was 5%. Nontreatment factors, such as liver tumour volume and metastases to the portal lymphatic nodes, had a dominating survival influence, and should be stratified for in controlled trials. Arterial thrombosis was a common complication, and correlated positively with survival. Treatment morbidity, including abscess formation, bleeding, and aneurysm, was substantial, especially after combined treatment with temporary dearterialisation.

Intraperitoneal infusion of 5-FU made the drug delivery easy and safe. Continuous intraperitoneal infusion of 5-FU gave stable and reproducible levels of the drug in the peripheral venous blood and the calculated intraperitoneal concentration was about 600 times higher. This implicates that IP chemotherapy should be beneficial in adjuvant

treatment, when intra-abdominal recurrent disease may be expected. The effect on established liver disease was apparently comparable to that obtained with hepatic arterial infusion, but the benefit remains to be documented in a controlled trial.

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MAJOR LIVER RESECTION -

PERIOPERATIVE COURSE AND MANAGEMENT

Henrik Ekberg, MD, Karl-Göran Tranberg, MD PhD, Roland Andersson, MD, Bengt Jeppsson, MD PhD, Stig Bengmark, MD PhD.

From the Department of Surgery, Lund University, Lund, Sweden.

Correspondence:

Henrik Ekberg, M.D.
Department of Surgery
Lund University
S-221 85 Lund
Sweden

ABSTRACT

This report investigates the perioperative course in 81 consecutive major liver resections, performed mainly because of primary liver cancer or colorectal liver secondaries. The liver was resected transabdominally with or without prior ligation of hilar structures. Intravenous nutrition consisted of 10% dextrose alone and was started preoperatively. Albumin or plasma was used rarely and only in conjunction with massive intraoperative transfusion of blood. Major complications, including 4 operative deaths (4.9%), consisted of bleeding and/or infection in 8 (10%) patients and overt liver failure in 2 (2%) and occurred only after right and extended right lobectomies. Intraoperative blood loss was significantly larger in patients with postoperative complications than in patients with an uneventful postoperative course. The direct parenchymal approach was associated with a shorter operation time and an unchanged intraoperative bleeding. Coagulopathy and hypoalbuminemia did not cause any problems. Blood glucose levels were stable and no patient suffered from hypoglycemia. It is concluded that major liver resection should be based on prevention of intraoperative bleeding and that preresection ligation of hilar structures offers no advantage in this respect. Infusion of hypocaloric glucose solutions should be started the day before operation and routine administration of other nutrients does not seem necessary.

INTRODUCTION

Numerous reports deal with the indications and techniques for major hepatic resection, whereas only a few focus on the metabolic course and the nutritional management. Resection induces derangements of liver function that persist for several days or weeks depending on the size of the resection (1-4). The postoperative course may be complicated by bleeding (mechanical or caused by clotting disturbances) or infection as well as metabolic derangements such as hypoglycemia and liver failure (5-7). This report evaluates the intra- and postoperative course and management, with focus on metabolic changes and nutrition, in patients undergoing major liver resection.

MATERIALS AND METHODS

Patients

We reviewed the charts for all patients who underwent liver resection for liver tumour at the Department of Surgery, Lund University, Sweden, from 1976 to 1984. The study included 81 patients (34 men and 47 women) with a median age of 59 (range 27-74) years. Seventy-four patients had malignant disease (hepatocellular carcinoma, 9; cholangiocarcinoma, 8; mixed primary liver cancer, 3; colorectal liver metastases, 44; other liver secondaries, 10) and 7 patients had a benign liver tumour. None had liver cirrhosis. Only 13 (16%) of the patients had noted loss of weight before operation.

Preoperative management

All patients received intravenous glucose (100 g) the night before operation. Only 1 patient received total parenteral nutrition before operation. Fifty-seven of the patients were given prophylactic antibiotics which consisted of ampicillin, cephalosporine or tetracycline.

Intraoperative management

Anaesthesia was based on droperidol (Dridol^R), fentanyl (Leptanal^R), and pancuronium bromide (Pavulon^R). Fentanyl was occasionally replaced by pethidine, and droperidol by thiopentone, but these modifications did not appear to influence the per- or postoperative course. The median anaesthetic time was 6 h (range 1h45'-11h50'), while the median duration of the operation was 4h45' (range 1h-10h30'). Intermittent positive pressure ventilation was used during the operation and continued until the morning of the following day.

The operations consisted of 10 left lateral segmentectomies, 20 left lobectomies, 37 right lobectomies and 14 extended right lobectomies. A right- or leftsided transrectal incision was used in 62 patients, whereas subcostal or midline incisions were used in the remaining 19 patients. The liver transection was made bluntly with hemostats or occasionally with fingers ("finger fracture" technique). All vessels and bile ducts were individually ligated or cauterized, and no mattress sutures were used. Hilar vessels and bile ducts to the resected lobe were ligated ("preresection ligation") before division of the liver parenchyma in 29 cases, whereas no preresection ligation was used in the remaining 52. Clamping of the portal vein or hepatic artery was not used. A percutaneous transhepatic catheter was used for both pre- as well as postoperative decompression of the biliary tract in the 5 patients that were jaundiced before operation. These patients had a hilar cacina and received a bilio-enteric anastomosis in addition to the liver resection. Liver resection was combined with hepatico-choledochostomy and T-tube choledochostomy in 2 patients, with primary liver cancer close to the liver hilum. The operations were performed by 17 different surgeons. Many of those were surgeons in training, and 43 operations were led by the senior author (S.B.).

Intraoperatively, 2000 (median, range 500-4000) ml of Ringer's solution and 110 (median, range 50-260) g of glucose in water were infused. The median number of units of whole blood or erythrocyte concentrate given was 8 (range 0-42). As a rule, fresh frozen plasma was administered after every third unit of stored whole blood or concentrate of erythrocytes. Two to 4 units of platelets concentrates were given after the first 6 units of blood, and additional platelets were given when the platelet count was lower than 60 000.

Postoperative management

Only a few patients were given albumin and then in small quantities (Fig. 1). Plasma was given to patients receiving massive transfusion of blood. A median of 6,5 l of crystalloids containing 275 g of glucose was administered during the day of operation. A median of 200-250 g of glucose in 3 l of water and electrolytes was infused daily for the next 3 days and was followed by increasing oral intake of fluids and food (Fig. 2). Most patients started to eat within 4 days and all but 2 of the (surviving) patients had resumed eating within 8 days. I.v. infusion was usually discontinued after 6 days (range 2-25), and only 7 patients received infusions for more than 10 days. Postoperative complications led to the use of total parenteral nutrition in 4 patients.

Fig. 1.
Administration of plasma
and albumin during ope-
ration and for the first 8
postoperative days (median
values). Hatched bars indi-
cate number of patients.

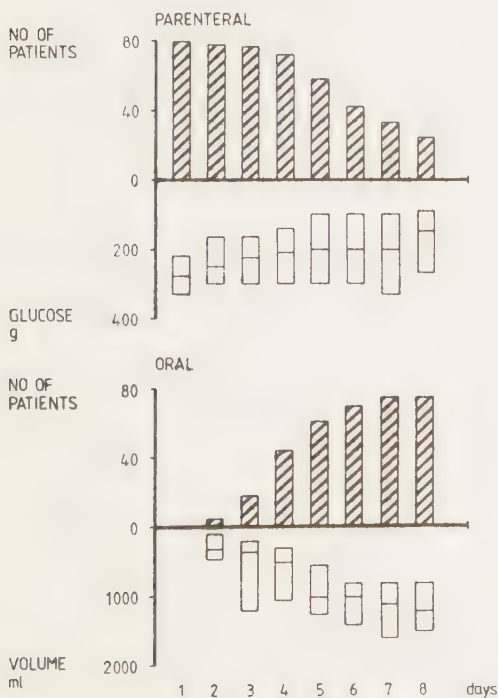
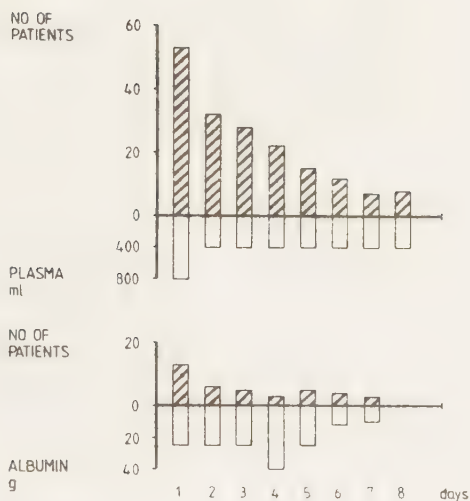


Fig. 2.
I.v. glucose and oral
nutrition during operation
and for the first 8 post-
operative days. Values are
medians and interquartile
ranges. Hatched bars indi-
cate number of patients.

Statistical methods

Differences between groups were tested with the Mann-Whitney rank sum test for unpaired data. Correlation was evaluated by calculation of the Spearman rank correlation coefficient (r_s). Possible differences in frequency were tested with the chi-square test. Values are medians and ranges, unless otherwise stated.

RESULTS

Laboratory tests

Laboratory tests are summarized in Table 1. There was a sharp rise of the transferases (alanine aminotransferase, ALAT; asparatate aminotransferase, ASAT) that normalized within a week. Bilirubin also increased rapidly but returned more slowly to normal. Blood levels of alkaline phosphatases (ALP) and γ -glutamyltransferase (GT) showed an initial moderate decline and then increased to normal during the first week.

The initial elevations of bilirubin and transferases varied with the amount of liver resected. Bilirubin was significantly higher after right lobectomies than after leftsided resections during the first 5 postoperative days ($p < 0.01$ at all time points; Fig. 3). A similar difference was noted for transferases during the first 2 postoperative days ($p < 0.001$ and $p < 0.05$, respectively). Other laboratory data such as ALP, GT, albumin, creatinine, glucose, potassium, sodium, and activated partial thromboplastin time (APTT) were not influenced by the extent of liver resection.

Table 1. Laboratory tests (medians and interquartile ranges)

	Preop	Day 1	Day 3	Day 5	Day 7
Bilirubin	9	52	48	38	24
umol/l	(6-11)	(24-81)	(29-71)	(16-68)	(18-82)
ALP	5.6	3.3	3.9	4.4	5.4
ukat/l	(3.6-7.6)	(2.8-4.1)	(3.4-5.0)	(3.2-6.1)	(4.1-8.1)
ALAT	0.4	3.3	2.3	1.1	1.4
ukat/l	(0.2-1.6)	(1.6-5.4)	(1.4-3.6)	(0.7-2.1)	(0.6-1.8)
Glucose	7.1	7.2	6.0	5.1	5.4
mmol/l	(4.8-9.6)	(5.5-9.0)	(4.9-7.5)	(4.8-7.0)	(4.9-7.2)
Albumin	37	33	28	32	34
g/l	(36-40)	(30-36)	(24-32)	(27-33)	(27-42)
Thrombocytes	255	120	117	135	195
10 /l	(200-315)	(95-185)	(85-140)	(105-215)	(80-225)

ALP = alkaline phosphatases; ALAT = alanine aminotransferase.

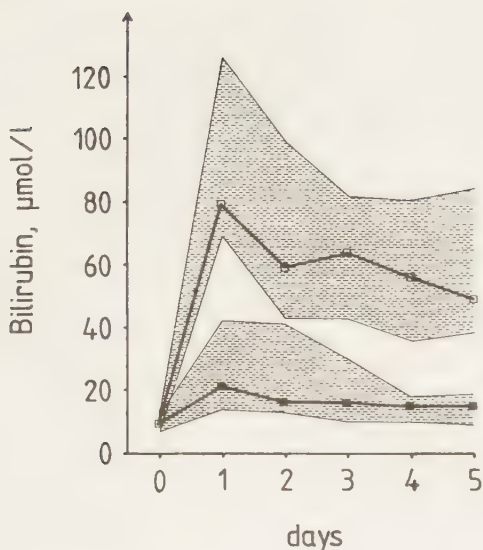


Fig. 3.

Comparison of bilirubin after right- (open squares) and leftsided (closed squares) resections. Values are medians and interquartile ranges ($p < 0.001$ at all time points).

We did not encounter any instance of hypoglycemia; blood glucose was quite stable and usually between 5-10 mmol/l. Serum albumin showed an immediate and moderate fall and did not start to rise significantly during the first week (Table 1).

The 5 patients with preoperative jaundice because of tumour in the liver hilum were excluded from the analyses of laboratory data. Also excluded was a patient who received a porta-caval shunt (see below).

Bleeding disorders

The amount of blood transfused increased with the amount of liver resected; left lateral segmentectomies required 2.5 (1-9), left lobectomies 5 (0-12), right lobectomies 12 (5-42), and extended right lobectomies 11 (6-25) units of blood during and after surgery. Intra- and postoperative massive bleeding (requiring more than 30 units of blood intra- and postoperatively) was encountered in 6 patients.

The platelet count fell markedly for the first 2 days after operation and then increased slowly to normal values (Table 1). The platelet counts 24 h after surgery varied negatively with the amount of intraoperative transfusion of blood (Fig. 4; $r_s = -0.60$, $p < 0.001$). Also, the fall in platelet counts was more pronounced after right lobectomy than leftsided resections ($p < 0.001$ for the first 2 postoperative days). APTT did not vary between the groups, and it was generally stable during the first postoperative week.

Preresection ligation

This procedure was used in 8 left- and 21 rightsided lobectomies. In right and extended right lobectomies ($n=51$), preresection ligation was associated with an increased operation time, as compared to the direct parenchymal approach (5.7 (4-11) vs 4.6 (2-10)h; $p < 0.001$). There was no significant difference in intraoperative blood transfusion (11 (6-42) vs 12 (5-32) units; $p > 0.05$). The type and rate of complications after preresection ligation were similar to that after the direct parenchymal approach.

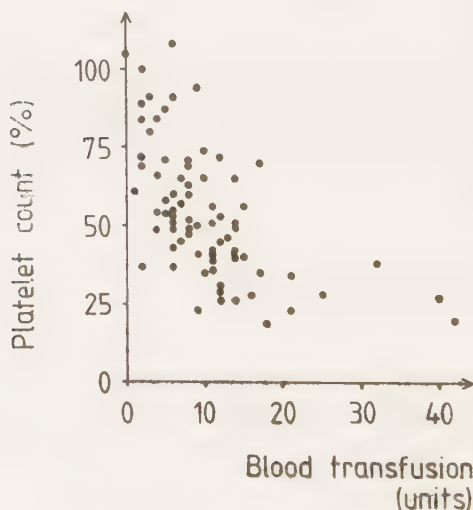


Fig. 4.
Relationship between intraoperative blood transfusion and the platelet count 1 day after surgery (expressed as a percentage of the preoperative value; $r_s = -0.60$, $p < 0.001$).

Complications

Operative mortality (4.9%) was seen after right-sided resections alone. Technical difficulties during right lobectomy in massive tumors led to bleeding from the caval vein with 1 intra-operative death and 1 death 11 days post-operatively. Another patient undergoing right lobectomy died in liver failure 15 days after surgery because of necrosis of a large part of the remaining liver (autopsy did not reveal the cause). Finally, 1 patient bled to death from a duodenal ulceration 46 days after extended right lobectomy complicated by intraabdominal abscess formation.

The main portal trunk was accidentally divided in 1 patient, and required an end-to-side porta-caval shunt before resection. The postoperative course was uneventful.

Major complications were encountered in 14 (17%) patients (bleeding or abscess leading to death or reoperation, leaking bilio-digestive anastomosis, and liver failure). A total of 27 (33%) patients had postoperative complications (Table 2). Except for 3 with pneumonia, respiratory insufficiency, or wound rupture, all had been operated on with a right or an extended right lobectomy for cancer.

Table 2. Postoperative complications

	No. of patients	Type of resection

Abdominal	20(25%)	
Reoperation, bleeding	3	RL(3)
Reoperation, abscess	5	ERL,RL(4)
Reoperation, no abscess	2	RL(2)
Reoperation, collection of bile	3	ERL(3)
Transient encephalopathy	2	RL(2)
Liver insufficiency	2	ERL,RL
Leaking hepatico-jejunostomy	3	ERL(2),RL
Bleeding duodenal ulcer	1	ERL
Wound rupture	1	LL
Pulmonary	19(23%)	
Hydrothorax	11	ERL(3),RL(8)
Pneumothorax	3	RL(3)
Pneumonia	2	RL,LL
Respiratory insufficiency	3	RL(2),LL
Total no. of patients with postoperative complications	27(33%)	

ERL=extended right lobectomy; RL=right lobectomy; LL=left lobectomy.

Patients with postoperative complications had a larger amount of bleeding during operation than patients with an uneventful postoperative course ($p < 0.001$).

Three patients were reoperated because of bleeding, whereas in an additional 5 cases reoperations were performed because of a proven abscess. Another 5 patients were thought to have an intraabdominal abscess; however, laparotomy revealed only some accumulation of bile in 3 and normal findings in 2 patients. A leaking bilio-digestive anastomosis complicated the postoperative course in 3 patients with hilar cholangiocarcinoma.

Two patients had overt liver insufficiency. One of them suffered from extensive necrosis of the remaining liver and supportive treatment was futile (see above). The other patient was jaundiced before surgery of a cholangiocarcinoma in the liver hilum. The operation consisted of an extended right lobectomy in combination with an anastomosis between jejunum and the left lateral segmental biliary duct. The patient demonstrated typical signs of liver failure with coma, elevated ammonia levels, electroencephalographic abnormalities and a deranged blood amino acid pattern shortly after surgery. Treatment included intensive monitoring, administration of amino acid solutions enriched with 45% branched-chain amino acids (BCAA) and plasmapheresis. The latter procedure was performed daily for 10 days and caused a dramatic decrease in blood ammonia and amino acids. The syndrome of liver failure disappeared within 20 days. Two patients had mild and transient encephalopathy post-operatively and were not given any specific treatment.

After surgery, 22 (27%) patients were treated in the Intensive Care Unit for a duration of 3 (1-24) days. The post-operative hospital stay was 13 (5-66) days, including the time spent after return to the referral hospital. The postoperative hospital stay varied with both the amount of blood transfused during operation ($r_s = 0.58$; $p < 0.001$) and the operation time ($r_s = 0.48$; $p < 0.001$).

Survival

Survival figures are given in Table 3. The survival for patients with hepatocellular and cholangiocellular carcinomas was 30 (9-62) and 10 (5-64) months, respectively. Three patients had a mixed form of primary liver cancer and two are still alive at 78 and 113 months. Resection of colorectal liver secondaries gave a survival of 20 (5-110) months and several long-term survivors.

Table 3. Survival (medians and ranges)

Diagnosis	No. of patients	Survival mo	Alive no. at mo
Primary liver cancer			
Hepatocellular	8	30(9-62)	2 at 48,62
Cholangiocellular	7	10(5-64)	0
Mixed	3	78(12-113)	2 at 78,113
Secondary liver cancer			
Colorectal	41	20(5-110)	13 at 8,8,8, 10,15,22,26 29,35,50, 68,95,110 1 at 72
Malignant melanoma	3	19(5-72)	1 at 72
Squamous cell cancer	2	23(18-27)	0
Gallbladder cancer	2	52(30-73)	1 at 73
Pancreatic cancer	1	13	1 at 13
Adrenal cancer	1	17	1 at 17
Carcinoid	1	72	0

DISCUSSION

Recent reports show that major liver resection is associated with an operative mortality rate of 4-20% at institutions that are relatively well experienced in this kind of surgery (8-11). It is clear that the intra- and postoperative management of these patients needs further refinement.

Although coagulation defects can always be demonstrated after liver resection (5), we did not have any case in whom intra- or postoperative bleeding could be ascribed to a deficiency in the hepatic production of clotting factors. We believe that the absence of non-mechanical hemorrhage was due to the liberal administration of fresh whole blood, fresh frozen plasma and, probably most important, fresh platelet concentrates. This regimen was effective even if the bleeding as well as the fall in platelet counts was substantial (Fig. 4). However, even if non-mechanical hemorrhage can be controlled, the present study demonstrated that (mechanical) hemorrhage was a major determinant of mortality and complications. Recent studies suggest that new technical modalities such as the ultrasonic dissector would be helpful in this respect (12).

In the liver transections we used either the primary parenchymal approach with intrahepatic ligation of all vessels or the technique of preceding vascular control

(preresection ligation) of hilar structures. Preresection ligation has been suggested to give a better control and therefore less bleeding (13). On the other hand, it carries the risk of erroneous ligation of hilar vessels (13), should partially denervate the liver with possible risk of increased bleeding (14), and produces a period of warm ischemia that may be harmful (15). We found that the extent of bleeding was similar after the two procedures. The only difference was that preresection ligation increased the operation time. Therefore, we believe that the direct parenchymal method should be preferred to the technique of preresection ligation.

Two patients suffered from fulminant hepatic failure. In the patient who died, it was associated with a large area of necrosis in the remaining liver. Although the cause was not revealed, it might be relevant that the technique of pre-resection ligation had been used. The other patient had a Klatskin tumour, was deeply jaundiced before operation (despite pre-operative percutaneous drainage) and underwent an 85% hepatectomy. The subsequent liver coma was treated immediately and reversed after 3 weeks of intensive therapy with plasmapheresis. The rationale for the plasmapheresis was to remove potential toxins that might disturb the regenerative capacity of the liver cells (16). It had impressive effects on blood levels of ammonia, bilirubin, liver enzymes and amino acids in our patient. The decrease in ammonia may be particularly relevant because it has been demonstrated that ammonia can inhibit liver regeneration in rats (17). However, our experience, as that of others (18), does not yet allow any definite statements about the role of this treatment in liver failure.

Unfortunately, there is no test that accurately predicts the risk of liver failure in the pre- or postoperative situation (7). In the postoperative period, we look for deviations in serum bilirubin from the normal pattern as an early sign of liver insufficiency. As demonstrated in this study, the rise in bilirubin depends on the extent of resection (Fig. 3). It peaks during the first postoperative week and should normalize within the next two weeks (1,4,19).

Considering the half-life of albumin (about 17 days (20)), a decreased synthesis cannot be the sole explanation for the rapid and considerable decrease in serum albumin. Other factors must play a role, and likely candidates are loss of blood and plasma, dilution, leakage of protein from the raw liver surface, and, perhaps most important, transcapillary leakage. Whatever the cause, the decrease in albumin was without clinical importance in this study. Today we would consider albumin repletion only when the albumin level is so low that the patient is at risk of developing interstitial edema due to the decrease in plasma oncotic pressure.

However, even this idea was recently challenged by Grundman and Heisterman, who could not find evidence for a beneficial effect of albumin administration in a prospective study of ICU patients with a low (<24 cm water) colloid osmotic pressure in plasma (21).

Hypoglycemic problems are encountered mainly after extensive liver resections or in connection with severe complications such as sepsis. It is presumably due to the removal of liver parenchyma, and thus liver glucogen, together with a decreased absolute capacity for gluconeogenesis and a surgically induced depletion of glycogen in the remaining liver. This complication can generally be prevented by giving hypocaloric glucose solutions for the first postoperative days, but it may not be enough (22). The fact that we did not experience any episode of hypoglycemia in our patients is attributed to our policy of filling the glycogen stores preoperatively by glucose infusion. Another argument for giving glucose before operation is that the resistance of liver respiration to anoxia is increased by glucose before, but not after, the anoxic period (23). It may also be speculated, that preoperative glucose administration makes it easier to avoid hypoglycemia without the risk of excessive levels of glucose and insulin and subsequent low levels of free fatty acids. In the rabbit, the remnant liver seems to depend almost exclusively on oxidation of free fatty acids during the first postoperative day after 70% hepatectomy (24).

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DETERMINANTS OF SURVIVAL
IN LIVER RESECTION FOR
COLORECTAL SECONDARIES

H. Ekberg, M.D., K.-G. Tranberg, M.D., Ph. D, R. Andersson,
M.D., C. Lundstedt, M.D., I. Hägerstrand, M.D., Ph. D., J.
Ranstam, B.Sc., S. Bengmark, M.D., Ph. D.

From the Departments of Surgery, Diagnostic Radiology and
Pathology, Lund University, and the Southern Swedish
Regional Tumour Registry, Lund, Sweden.

Correspondence:
Henrik Ekberg, M.D.
Department of Surgery
Lund University
S-251 85 Lund
Sweden

All 72 resections for colorectal liver secondaries during the period 1971-1984 were analysed retrospectively. Liver tumours were single in 35 (49%), unilateral in 55 (76%) and associated with extrahepatic disease in 12 (18%) patients. Operative mortality was 5.6%.

With respect to the disease in the liver, the presence or absence of 4 or more metastases was the predominant prognostic determinant with a 5-year survival rate of 20% in patients with less than 4 liver tumours, and no 3-year survivor among patients with 4 or more tumours. When the number of liver tumours was less than 4, unilateral disease tended to have a better prognosis than bilateral disease, but the difference was not significant ($p=0.19$). No other liver disease variable seemed to play any role for the prognosis. Extrahepatic disease was associated with a poor prognosis and no 5-year survivor. The length of the tumour-free resection margin was the only treatment variable that varied with the outcome: a resection margin of less than 10 mm was followed by a poor survival. Variables that did not influence survival included uni- or bilateral disease, liver tumour volume, tumour size, type of liver resection, Dukes' classification, differentiation of the primary tumour and synchronous or metachronous disease.

It is concluded, that resection for liver colorectal secondaries is indicated when a) liver tumours are less than 4, even if bilateral, b) no extrahepatic disease is present, and c) a resection margin of at least 10 mm can be obtained. It should not be performed unless all of these requirements are met.

Key words: Liver neoplasms, surgery, liver resection, indication, prognosis

INTRODUCTION

Using current indications for liver resection, it may be estimated that 5-10% of all patients with colorectal cancer are candidates for surgery against metastatic disease in the liver. This means that in the US alone 6,000-12,000 patients are candidates for curative liver surgery each year. However, the 5-year survival rate is about 20-30% (1,2), which indicates that the majority of patients are not helped by the operation. Adson and van Heerden (3) estimated 20-30% of their patients to benefit from liver resection, in terms of prolonged survival and/or quality of life. There is obviously a need for better identification of patients likely to benefit from liver resection.

This report aims at providing improved guidelines for treatment selection before and during surgery. To this end, we investigated the prognostic determinants in a comparatively large, consecutive series of liver resection for colorectal secondaries.

MATERIAL AND METHODS

This is a retrospective study which includes all 72 patients undergoing liver resection for metastases from colorectal cancer at the Department of Surgery, Lund University, Sweden, during the period 1971-1984. Thirty-six of the patients were male and 36 were female with a median age of 62 (range 27-76) years *.

Disease characteristics

The primary tumour was excised from the rectum in 21 (29%) patients and from the colon in 51 (71%) cases. It was well differentiated in 7 (10%) patients, moderately in 57 (79%) and poorly in 8 (11%). In 3 (4%) patients the tumour was classified as Dukes A, in 19 (26%) as Dukes B and in 50 (69%) as Dukes C. The hepatic tumours were well differentiated in 3 (4%) patients, moderately in 64 (89%) and poorly in 5 (7%). All histologic slides were reviewed.

The liver metastases were synchronous in 41 (58%) patients. For 31 patients with metachronous liver metastases the median disease-free interval was 19 (3-87) months. The liver metastases were unilateral in 55 (76%) patients and bilateral in 17 (24%) patients. There was a single metastasis in 35 (49%) patients, multiple widespread deposits in 26 (36%) patients and one large tumour with small satellites around it, in the same liver segment, in 11

* Throughout the paper, values are medians and ranges.

(15%) patients. The total number of metastatic deposits was 1 in 35 patients; 2 in 16; 3 in 7; 4 in 7; 5 in 4; 6 in 2 and 10 in 1 patient. The diameter of the largest metastasis was 5 (1-21) cm. Data on number and size of metastases were taken from histopathology and/or laparotomy findings.

Preoperative angiography was performed in most patients. Fifty angiograms could be reviewed and were used for classifying the extent of liver involvement, in per cent of the total liver volume, into 3 groups: <25% (I), 25-49% (II), and 50-74% (III). In the remaining 22 cases (mainly wedge resections) the tumour volume estimation was based on laparotomy findings. Forty-one (57%) patients belonged to group I, 23 (32%) to group II and 8 (11%) to group III. Liver function tests were elevated in most patients: alkaline phosphatases in 55%, γ -glutamyl-transpeptidase in 35%, and aspartate-aminotransferase in 19%. No patient had elevated bilirubin.

Treatment

Major liver resection was performed in 59 (82%) patients (Table 1). The time from diagnosis to resection was 2 (0.7-15) months. Thirteen (18%) patients had wedge resection only, and their tumours were excised synchronously with the primary tumour. In the 17 cases with bilateral tumour, major liver resection was combined with wedge resection in the contralateral lobe in 10 patients, bilateral wedge excisions were performed in 4, and an extended lobectomy in another 3.

Altogether 12 (17%) patients had extrahepatic disease, which involved two extrahepatic sites in 4 of them. Dissection of the hepatoduodenal ligament, with removal of

Table 1. Type of liver resection

	no.	%
Left lateral segmentectomy	6	8
(with right wedge	1)	
Left lobectomy	8	11
(with right wedge	3)	
Extended left lobectomy	1	1
Right lobectomy	32	44
(with left wedge	4)	
Extended right lobectomy	9	13
(with left wedge	1)	
Various segmentectomies	3	4
(median segment with right wedge	1)	
Wedge excision only	13	18
(bilateral wedge	4)	
(multiple unilateral wedge	2)	
Total	72	100

lymph glands for microscopic examination, was performed in 31 (43%) patients, and revealed lymph node metastases in the liver hilum in 6 and around the coeliac axis in 2. The remaining extrahepatic intra-abdominal manifestations consisted in overgrowth to the diaphragm (2) or the vena cava (1) and deposits in the ovaries (2). Three patients had lung metastases known at the time of the liver operation, and pulmonary resection was performed later.

Histologic examination of the liver specimen showed tumour growth in the resection margin in 14 (19%) cases, tumour growth within 10 mm from the cut margin in 30 (42%) cases, and a tumour-free margin of more than 10 mm in 28 (39%) cases.

Postoperative adjuvant treatment with cytotoxic drugs was given to 8 (11%) patients. Another 25 (35%) patients recieved cytostatic therapy for palliation of recurrent disease in the liver or elsewhere. The drugs and route of administration varied. Thirty-nine patients did not receive any cytotoxic treatment.

The follow-up time after liver resection was 20 (3-167) months.

Definitions

Postoperative mortality: Death within one month or before the patient left hospital.

Survival: Interval from liver resection to death. Cases of operative mortality were excluded from the analyses of prognostic factors. Survival times are actuarial.

Size and number of metastases: Tumours were classified as "small" when the largest diameter was < 4 cm and as "large" when it was $\geq$ 4 cm. The term "multiple" signifies 2 or more tumours as opposed to 1 ("single"), whereas "solitary with satellites" denotes a large tumour closely surrounded by one or more small tumours in the same segment of the liver. The term "multiple large" denotes that one or more tumours had a diameter of $\geq$ 4 cm.

Statistical methods

Therapeutic and other factors that may have influenced the survival were tested for statistical significance both separately and simultaneously. Survival curves were constructed with the life table technique. The Generalized Wilcoxon test (4) was used to analyze the influence of isolated variables on survival. In the multivariate analysis, Cox' proportional hazards model (5) was used to determine the importance of each variable at the same time

as the influence of the other, possibly interrelated, variables were taken into account. In this analysis, all variables were entered and then selected stepwise in order of statistical significance.

RESULTS

The overall median survival time was 22 (0-167) months, including the operative mortality. Survival was 81% after 1 year, 30% after 3 years and 16% after 5 years. All variables analyzed in the single and multivariate analyses are given in Table 2.

Determinants of survival tested separately

Table 3 and Figs. 1-4 summarize the results and include all the variables that were found to be significantly associated with differences in survival.

Table 2. Variables entered into the single-variable and the multivariate analyses.

Number of hepatic tumours;	single or multiple (< 4 or > 4) (actual number) *
Intrahepatic distribution;	uni- or bilateral disease
Margin of resection;	0 or > 0 , < 10 or > 10 mm ** (< 10 or ≥ 10 mm) *
Tumor size;	cm
Number and size combined;	n=1; size < 4 cm or > 4 cm ** n>1; size < 4 cm or ≥ 4 cm **
Extrahepatic metastases;	yes or no
Liver resection;	wedge or major
Site of primary cancer;	colon or rectum
Dukes' classification;	A,B or C
Differentiation of the primary;	high, moderate or low
Synchronous liver metastases;	yes or no
Sex;	male or female
Cytostatic treatment;	adjuvant, palliative or none
Bilirubin;	mmol/l *
y-glutamyl-transpeptidase;	μ kat/l *
Alanine-aminotransferase;	μ kat/l *
Aspartate-aminotransferase;	μ kat/l *
Alkaline phosphatases;	μ kat/l *

When a variable was exchanged with a variable within parenthesis, no other deviation from the standard scheme was introduced in to the multivariate analysis.

* multivariate analysis only.

** single-variable analysis only.

Table 3. Single-variable analysis of possible prognostic factors (n=68).

Variable	No. of patients	Survival 3yr,%	5yr,%	p-value

NUMBER OF TUMOURS				
Single vs multiple				
1) single	34	45	24	0.05 (1vs2)
2) multiple	34	22	9	
3) solitary with satellites	10	0	0	0.01 (1vs3)
< 4 vs > 4 tumours				
1) 1,2 or 3	55	41	20	0.03
2) 4 or more	13	0	0	
INTRAHEPATIC DISTRIBUTION				
1) Unilateral	52	37	17	0.14
2) Bilateral	16	18	18	
< 4 tumours				
1) Unilateral	44	42	20	
2) Bilateral	11	20	20	
NUMBER AND SIZE				
1) single small	14	50	40	0.01 (1vs4)
2) single large	20	43	11	
3) multiple large **	20	26	13	
4) multiple small	14	14	0	
TUMOUR VOLUME				
1) <25%	41	39	24	0.01 (1vs3)
2) 25-49%	22	33	7	0.01 (2vs3)
3) 50-74%	5	0	0	
EXTRAHEPATIC METASTASES				
1) not present	56	36	20	0.01
2) present	12	10	0	

* p-values > 0.15 omitted.

** one or more tumours have a diameter ≥ 4 cm.

Survival was significantly better in patients with single than with multiple liver metastases. A solitary metastasis with satellite nodules was associated with no 3-year survival and a worse prognosis than a truly single tumour. If tumour spread was unilateral ($n=52$), patients with a single tumour tended to live longer than patients with multiple metastases, but the difference was short of statistical significance ($p=0.11$; Fig. 1).

Patients with 1, 2, or 3 liver tumours had a better prognosis than those with 4 or more among whom there was no 3-year survivor regardless of whether the disease was unilateral ($n=8$) or bilateral ($n=5$) (Fig. 2). In patients with less than 4 tumours and bilateral disease ($n=11$) both the 3- and 5-year survival rates were 20%. Corresponding figures for unilateral disease ($n=44$) were 42% and 20%, giving a survival that was not significantly longer than in bilateral disease ($p=0.19$; Fig. 3).

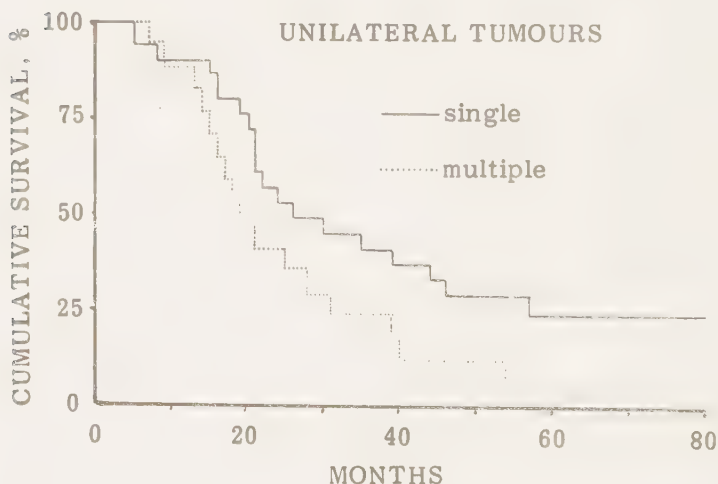


Fig. 1
Cumulative probability of survival for patients with unilateral liver tumours ($n=52$). The difference in survival between single (—, $n=34$) and multiple (..., $n=18$) metastases was not significant ($p=0.11$).

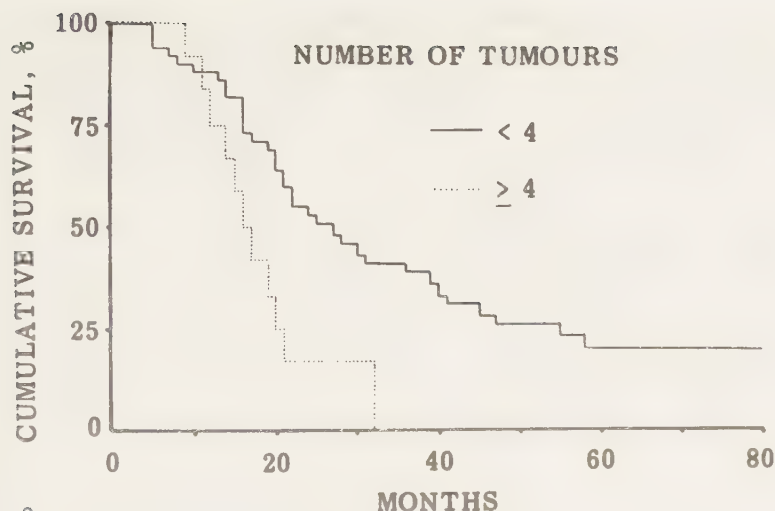


Fig. 2
The difference in cumulative probability of survival between < 4 (—, n=55) and ≥ 4 liver tumours (... , n=13) was significant ($p=0.03$).

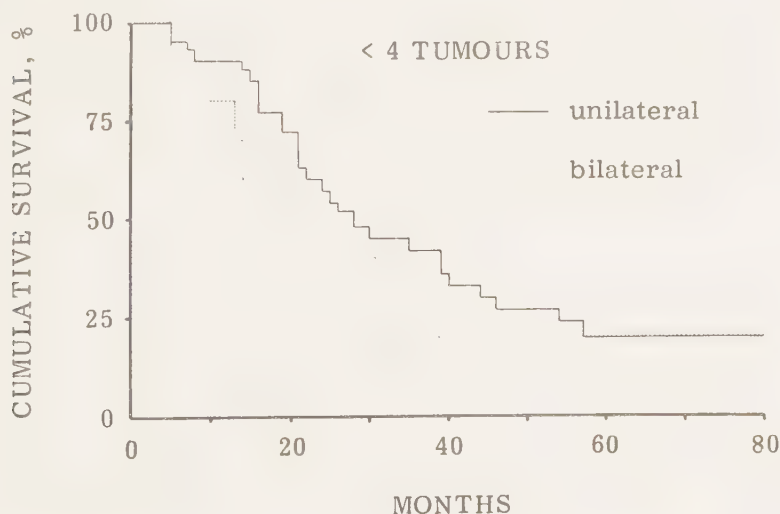


Fig. 3
Cumulative probability of survival in patients with less than 4 liver tumours. The difference in survival between unilateral (—, n=44) and bilateral (... , n=11) disease was not significant ($p=0.19$).

Disregarding the number of tumours, the presence of bilateral deposits tended to worsen the prospect of survival ($p=0.14$), although the 5-year survival rate (18%) was similar to that in unilateral disease (17%). If only patients with multiple metastases are considered, there was no difference in survival between uni- and bilateral spread ($n=34$; $p=0.46$).

Patients with a small single metastasis had the best prognosis with a 5-year survival rate of 40% and a significantly longer survival than those with multiple small metastases. Patients with a liver tumour volume exceeding 50% showed a worse prognosis than patients with less amount of tumour and no one lived for 3 years.

The presence of extrahepatic metastases, i.e., in the lungs, liver hilum or elsewhere had a significant impact on survival.

The extent of tumour-free margin was the only treatment variable that correlated with length of survival. Patients with a tumour-free margin of > 10 mm had a significantly longer survival than those with no free margin (Fig. 4).

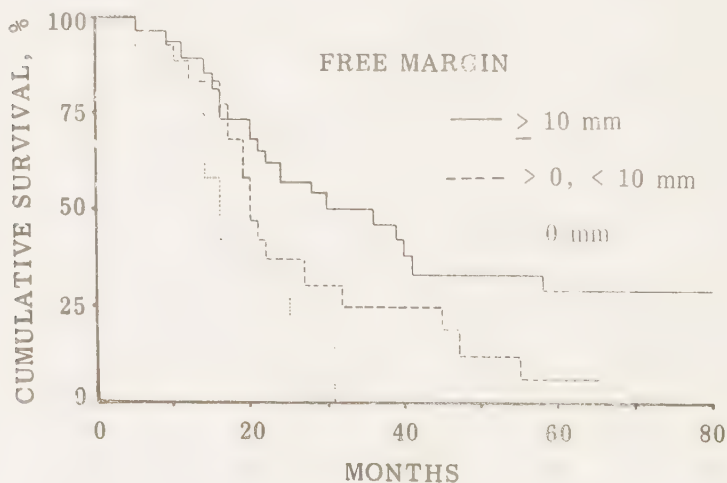


Fig. 4

Cumulative probability of survival according to the resection margin. The difference in survival between > 10 mm (—, $n=27$) and no margin (...., $n=12$) was significant ($p=0.03$).

Determinants of survival - multivariate analysis

In this analysis, only three factors were found to significantly decrease the chance of survival (Table 4): > 4 tumours, a tumour-free margin of less than 10 mm, and extrahepatic disease. The presence of any one of them doubled the risk of dying.

When the number of liver metastases was classified as a) single or multiple, b) the actual number observed, or c) single or multiple in unilateral disease, the number of tumour deposits had no statistically significant association with length of survival (p values about 0.20).

The negative impact of > 4 tumours was seen also when patients with unilateral disease alone were analyzed (n=52; p=0.05).

When the tumour-free margin was classified as either no free margin or a free margin of more than 0 mm, this variable was not significantly associated with length of survival (p=0.19).

Metachronous disease tended to increase the chance of survival (p=0.10). The following variables did not influence the prognosis: uni- or bilateral disease, liver tumour volume, tumour size, type of liver resection, site of primary cancer, Dukes' classification, differentiation of the primary cancer, sex, cytostatic treatment, and pre-operative liver function tests. Except for the influence of liver tumour volume this agreed with the findings in the single-variable analyses.

Table 4. Determinants of survival
(Cox proportional hazards model, n=68)

Variable	Status	Relative	
	1 vs 2	Risk 1:2*	p
Number of hepatic tumours	> 4 vs < 4	2.2	0.04
Resection margin	< 10 vs ≥ 10	2.0	0.05
Extrahepatic metastases	yes vs no	2.0	0.05

* The Relative Risk 1:2 estimates the increased risk of short survival in a patient with Status 1 as compared to a patient with Status 2, provided that all other variables in the analysis are kept constant.

Recurrence

Fourty-six (64%) patients died of recurrence. Seven (10%) patients are living with disease 9 (4-25) months after resection. Eleven (15%) patients are disease-free 47 (3-167) months postoperatively. Four patients died of intercurrent disease, and none of them showed evidence of tumour recurrence at autopsy.

Complications

Four patients died from the operation giving a total operative mortality of 5.6 % (Table 5). In 2 patients with extensive tumour growth around the vena cava, injury to the vein led to excessive bleeding and asystole. One of the patients died during the operation, the other 11 days later from cerebral ischemia. One patient died in liver failure 15 days after surgery because of necrosis of a large part of the remaining liver (autopsy did not reveal the cause). All 3 patients were operated on with right lobectomies. Finally, 1 patient operated on with extended left lobectomy never recovered from the postoperative liver insufficiency that followed and died 103 days after operation. During the postoperative period major complications were encountered in 11 (15%) patients.

Table 5. Complications

	no.	%
MAJOR		
Per-operative mortality	1	1.4
Post-operative mortality	3	4.2
Reoperation, bleeding	2	2.8
Reoperation, abscess	4	5.6
Reoperation, collection of bile	2	2.8
Reoperation, intestinal obstruction	1	1.4
Liver insufficiency	3	4.2
MINOR		
Transient encephalopathy	3	4.2
Suspect intra-abdominal abscess	3	4.2
Wound infection	2	2.8
Urinary tract infection	3	4.2
Pneumonia	1	1.4
Pleural effusion	9	12.5
Pneumothorax	2	2.8
Total no. of patients	26	36.1

DISCUSSION

This study supports the view that resection of colorectal liver secondaries is beneficial in patients with less than 4 liver tumours. In addition, it indicates that liver resection should not be performed in patients with 4 or more liver tumours or with extrahepatic disease. Finally, the study demonstrates that it is essential to obtain a margin of resection that is 10 mm or more.

With respect to the liver, the predominant prognostic determinant was the presence or absence of 4 or more metastases. When this factor was taken into account, other possible determinants, such as tumour size and liver tumour volume, assumed little or no importance. Four or more tumours carried a bad prognosis regardless of whether the disease was uni- or bilateral. When the number of tumours was less than 4, there was a tendency, although not significant, towards a better prognosis in unilateral disease.

In a study on the natural history of 466 patients with colorectal liver metastases, Wagner et al (6), considered 214 patients to be candidates for liver resection. Thirty-nine of these patients had a single metastasis and a notably high survival rate: 21% after 3 years and 3% after 5 years. Wood et al (7), reported a 3-year survival rate of 29% in a similar group of 7 patients. In these two studies, a few patients (6-17%) with unilateral multiple tumours lived for 3 years whereas none lived for 5 years.

Today, most surgeons would agree that a single colorectal tumour should be resected (8). Some surgeons would argue that resection is indicated also when lesions are multiple but confined to one lobe. Support for this contention can be found in studies demonstrating no difference in survival after resection of single or multiple lesions (1,9).

However, it is evident from our study that the simple categorization into one or multiple tumours was not helpful enough in distinguishing those patients with multiple tumours that may benefit from resection. It was not until we classified tumours as being less than 4 or not that much of the uncertainty was resolved. The idea to do so was first suggested by Goslin et al (10), who reported that patients treated with cytostatic drugs had a better survival if the liver tumours were less than 4. Similar results have also been reported after resection of liver tumours (11,12).

In our study, patients with less than 4 tumours had a 5-year survival rate of 20% regardless of whether the disease was uni- or bilateral. If the liver contained 4 or more tumours, no patient survived for 3 years, even if the tumours were

confined to one lobe. We believe that these survival rates allow the conclusion that patients with less than 4 tumours should be subjected to liver surgery and that the intrahepatic distribution of the disease does not influence this decision. Our figures likewise indicate that patients with 4 or more tumours should not undergo liver resection.

It has been reported that patients with multiple large tumours do better than those with multiple small tumours (1). Together with the importance of the number of tumours (particularly < 4 vs ≥ 4), this has led to the recommendation that every patient should wait for a few months before liver resection in order to let the "true nature" of the tumour disclose itself (12). Although we found that patients with multiple large tumours showed a slight tendency to do better than other patients with multiple deposits in the liver, we do not think that the value of a "test of time" has been demonstrated. First, patients with a single, small tumour had the best prognosis in our study. Second, it should be observed that the possible advantage of having a large tumour cannot be demonstrated unless it is allowed to grow either because liver involvement is not looked for or because a small tumour is being watched. In either case, the policy leads to a selection bias favouring patients with relatively large tumours since these patients originate from a pool of patients in which those with more aggressive disease have developed further metastases. We will continue to operate as soon as a preliminary diagnosis of resectable colorectal liver secondaries is made because we fear that the liver metastases may metastasize, for instance within the liver or to the liver hilum lymph nodes (13,14), while they are being watched.

The importance of looking for extrahepatic disease was underscored by the results obtained in dissection of the hepatoduodenal ligament and the coeliac axis: the 3-year survival was 0 in patients with, and 25% in patients without metastases in this area.

Investigators find that Dukes' classification of primary tumour influences survival (1,15) whereas others do not (9,11). We could not find a statistically significant variation with Dukes' classification, which, together with the reported discrepancy, implies that the influence is at most, slight.

In agreement with previous reports (11,15), we found that the presence of synchronous or metachronous disease did not influence survival. However, it is perhaps worth noting that metachronous tumours tended to do better ($p=0.10$) and that we recently reported that metachronous disease was associated with a significantly longer survival in patients

receiving hepatic arterial infusion of 5-fluorouracil (16). Thus, our figures do not exclude the possibility that metachronous tumour with a long disease-free interval signals a favourable prognosis. Whatever the truth, the influence of synchronous or metachronous disease, like that of Dukes' classification, is not strong enough to affect the decision to operate.

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PATTERN OF RECURRENCE
IN LIVER RESECTION FOR
COLORECTAL SECONDARIES

Henrik Ekberg, MD, Karl-Göran Tranberg, MD, PhD, Roland Andersson, MD, Christer Lundstedt, MD, Inga Hägerstrand, MD, PhD, Jonas Ranstam, BSc, Stig Bengmark, MD, PhD.

Departments of Surgery, Diagnostic Radiology and Pathology, Lund University, and Southern Swedish Tumor Registry, Lund, Sweden.

Reprint requests:
Henrik Ekberg, MD,
Department of Surgery
Lund University
S-221 85 Lund
Sweden

ABSTRACT

The pattern of relapse and factors influencing the site of recurrent disease were studied in 68 patients subjected to liver resection of colorectal metastases. Fifty-three (78%) patients had recurrence. Liver, lungs and peritoneal cavity were most frequently involved, and all patients with relapse had recurrence in one or more of these sites. Intra-abdominal relapse occurred in 50 (74%) patients (94% of patients with relapse). The liver was involved in 44 (65%) patients and was the only site of recurrence in 19 (23%). Extrahepatic metastases developed in 34 (50%) patients. Four or more liver tumors, a resection margin of less than 10 mm and extrahepatic disease were the main determinants of hepatic recurrence. Bilateral intrahepatic spread, as compared to unilateral disease, major liver resection, as compared to wedge resection, and per cent liver tumor volume were also associated with an increased risk of liver recurrence. The presence of extrahepatic disease before resection was the only factor that could be demonstrated to increase the risk of (further) extrahepatic spread. It is concluded that the number of liver metastases, the resection margin and the presence or absence of extrahepatic disease helps in predicting the risk of hepatic recurrence after resection for colorectal liver cancer. However, no variable presently available is of any help in predicting the extrahepatic recurrence affecting about half of the patients having no evidence of extrahepatic disease before liver resection. This finding should urge improved evaluation of candidates for liver resection and should influence adjuvant treatment protocols.

INTRODUCTION

After resection of colorectal liver metastases some three quarters of the patients die of recurrent disease (1,2). This is the reason why the present study investigates the pattern of recurrence and factors influencing the site of recurrent disease in patients subjected to resection of colorectal liver metastases. Such information is sparse and would aid in selecting patients for resection and would aid also in tailoring follow-up and postresection adjuvant treatment regimes.

MATERIALS AND METHODS

This is a retrospective analysis of a consecutive series of 68 liver resections for colorectal liver metastases during 1971-1984. Another 4 patients were operated during this period but were excluded from the present analysis because they died before discharge from the hospital (0-130 days after liver resection) (operative mortality: 5.6%).

Thirty-four patients were male and 34 female with a median age of 62 (range 27-76) years. The operations consisted of 13 (19%) wedge resections, 10 (15%) segmentectomies, 8 (12%) left lobectomies, 1 (1%) extended left lobectomy, 32 (47%) right lobectomies and 9 (13%) extended right lobectomies. Complete dissection of the hepatoduodenal ligament with removal of lymph nodes for microscopic examination was performed in 30 patients.

Nine patients were reoperated in the postoperative phase because of bleeding (2), abscess (4), bile leakage (2), and mechanical obstruction (1). Transitory hepatic insufficiency was encountered in 3 patients. Minor complications, infectious or respiratory, were encountered in 20 patients.

Enumeration of the liver tumors was based on histopathology and/or laparotomy findings. The margin of resection was determined from the histopathological review alone. The extent of liver involvement, in per cent of the total liver volume, was determined from preoperative angiograms in 50 patients and from laparotomy findings in 22 patients most of whom were treated with wedge resections.

The median follow-up time was 20 (range 3-167) months. Follow-up was standardized and based on clinical examination with rectoscopy and laboratory tests, including liver function tests and carcinoembryonic antigen (CEA), after 3, 6, 9, 12, 18, and 24 months and then at yearly intervals. Barium enema and/or colonoscopy and X-ray of the lungs were performed routinely after 1, 3 and 5 years. When the clinical or laboratory investigations suggested liver metastases, scintigraphy, ultrasonography and/or

computerized tomography (CT) combined with fine needle biopsy were performed. Other investigations, such as bone scintigraphy and CT of the pelvis, were carried out only when symptoms or laboratory findings indicated recurrent disease.

In each patient, extent of recurrence was determined on the basis of clinical, laboratory and radiologic investigation. In 23 (34%) patients it was based also on laparotomy findings at the time of initial relapse. Autopsy was performed in only 6 patients and did not give any new information with respect to the recurrence pattern.

Fifty-three patients had recurrence after a median disease-free period of 9 (range 1-36) months. Forty-six (68%) patients were dead with disease. Seven (10%) patients were living with disease median 9 (range 4-25) months after resection and 15 (22%) patients were disease-free after 47 (median; range 3-167) months. The proportions of patients dead with disease, and living with or without disease, at different time points are shown in Fig. 1. The overall median survival was 22 (0-167) months.

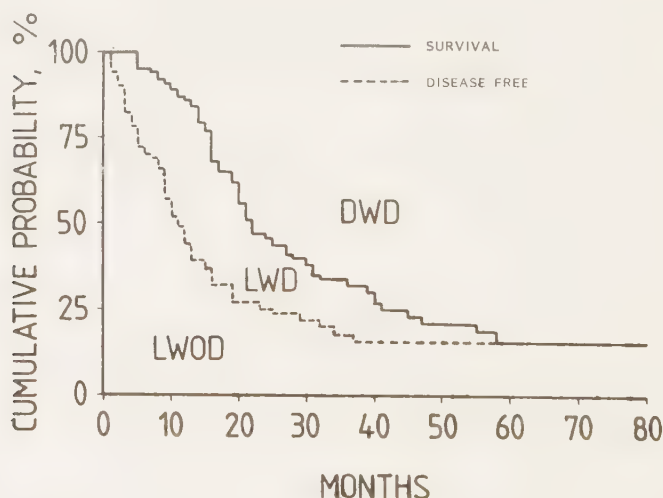


Fig. 1
Cumulative probability of survival (—) and of disease-free interval (---) after liver resection of colorectal metastases (n=72). LWOD = living without disease, LWD = living with disease, DWD = dead with disease.

Graphs of the disease-free interval were constructed with life-table technique. Possible determinants of recurrence (Table 1) were tested both separately and simultaneously. The Generalized Wilcoxon test (3) was used to analyze the influence of isolated variables on recurrence. In the multivariate analysis, Cox proportional hazards model (4) was used to determine the importance of each variable at the same time as the influence of the other possibly interrelated, variables were taken into account. In this analysis, all variables were entered and selected stepwise in order of statistical significance. Values are medians and ranges.

Table 1. Variables in uni- and multivariate analyses (n=68).

Variable	Definition	Patients n (%)
PRIMARY TUMOR		
Site	colon	48 (71)
	rectum	20 (29)
Differentiation	well	7 (10)
	moderate	54 (79)
	low	7 (10)
Dukes' classification	A	3 (4)
	B	18 (26)
	C	47 (69)
LIVER METASTASES		
Timing	synchronous	40 (59)
	metachronous	28 (41)
Intrahepatic spread	unilateral	52 (76)
	bilateral	16 (24)
Number of tumors	single	34 (50)
	multiple	34 (50)
	1, 2 or 3	55 (81)
	4 or more	13 (19)
Tumor diameter (largest)	< 4 cm	28 (41)
	> 4 cm	40 (59)
Liver tumor volume	< 25 per cent	41 (60)
	25-49 per cent	22 (32)
	50-74 per cent	5 (7)
Type of operation	wedge resection	13 (19)
	major resection	55 (81)
Margin of resection	> 10 mm	27 (40)
	< 10 mm	29 (43)
	no margin	12 (18)
EXTRAHEPATIC DISEASE		
Extrahepatic disease	not present	56 (82)
	present	12 (18)
Hilum node metastases	neg biopsy	24 (35)
	pos biopsy	6 (56)

RESULTS

The frequency of recurrent disease in different organs is summarized in Table 2. Fifty-three (78%) patients had relapse. The liver, lungs and peritoneal cavity (intra-abdominal lymph nodes, peritoneal surface) were most frequently involved and all patients with relapse had recurrence at one or more of these sites. Fifty (74%) patients (94% of those with relapse) had intra-abdominal recurrence, in the liver, peritoneal cavity or at the colorectal resection site. The liver was affected in 44 (65%) patients (83% of those with recurrent disease) and solely in 19 (28%) patients. Extrahepatic metastases were encountered in 34 (50%) patients and were unassociated with liver recurrence in 9 (13%) patients. The lungs were the most common site of extrahepatic recurrence and were affected in 15 (22%) patients. Three patients had pulmonary metastases only.

It is noteworthy that 8 (12%) patients had local failure. Four patients with colonic carcinoma had anastomotic recurrence 14 (8-35) months after the primary operation (10 (6-20) months after liver resection). The other 4 patients

Table 2. Sites of recurrence

Site	No. of patients	Per cent of all pat. (n=68)	Per cent of pat. with recurrence (n=53)
Liver (all)	44	65	83
Liver only	19	28	36
Extrahepatic (all)	34	50	64
Extrahepatic only	9	13	17
Lungs (all)	15	22	28
Lungs only	3	4	6
Local recurrence	8	12	15
Peritoneum *	12	18	23
Bone **	4	6	8
Skin **	4	6	8
Brain **	2	3	4
Extra-abdominal lymph nodes **	1	1	2

* Peritoneal surface and/or intraabdominal lymph nodes.

** Always combined with recurrence in the liver and/or other extra-hepatic sites.

had perineal and/or pelvic relapse 20 (10-30) months after resection of a rectal carcinoma (10 (5-14) months after liver resection). Five of the patients with local recurrence had liver secondaries synchronous with the primary tumor.

Liver recurrence was diagnosed 9 (1-57) months after liver resection; within a year in 68% of the cases and within 2 years in 89%. Lung metastases occurred after 17 (3-48) months; within a year in 33% and within 2 years in 67% (Fig. 2). Peritoneal recurrence was diagnosed after 14 (5-37) months. Patients with only extrahepatic metastases had the relapse after 16 (3-36) months. No patient developed recurrent disease more than 3 years after liver resection.

All variables that correlated significantly with disease-free interval in the single variable analyses are given in Table 3. The prognosis was unfavorable if there were multiple liver tumors and especially if the number of liver tumors was 4 or more. Bilateral hepatic disease was accompanied by earlier recurrence than unilateral disease. The difference was reduced, but still significant, when

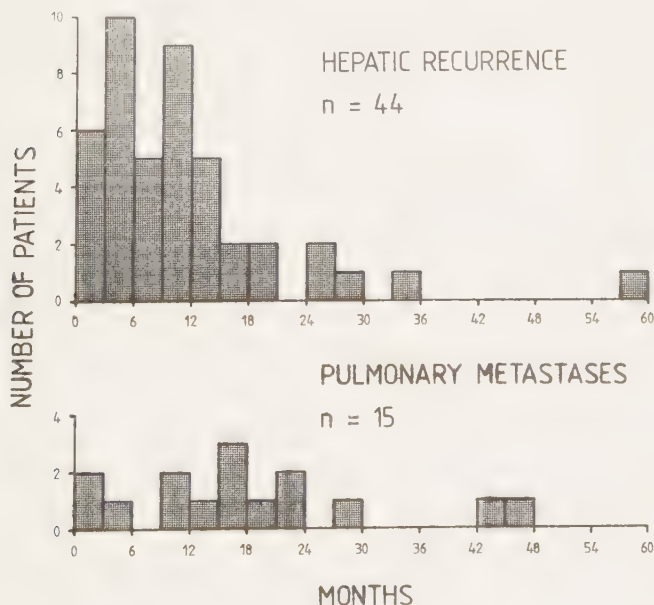


Fig. 2
Relapse in the liver and lungs at different time points after liver resection.

patients with multiple metastases only, (n=34) were considered (median 5 and 12 months, respectively; p=0.05). A similar difference was seen also in patients with < 4 tumors although the 3- or 5-year disease-free rates were only slightly higher in unilateral than in bilateral disease.

Table 3. Recurrence - single variable analyses.

Variable	No. of patients	Disease-free interval median, mo	3yr,%	5yr,%	p-value

NUMBER OF TUMORS					
Single vs multiple					
1) Single	34	16	24	24	0.01
2) Multiple	34	9	12	8	
< 4 vs > 4					
1) 1, 2 or 3	55	13	22	20	0.01
2) 4 or more	13	7	0	0	
INTRAHEPATIC SPREAD					
1) Unilateral	52	13	20	17	0.01
2) Bilateral	16	5	13	13	
< 4 tumors					
1) unilateral	44	16	24	21	0.04
2) bilateral	11	5	18	18	
LIVER TUMOR VOLUME					
1) < 25%	41	11	25	22	0.03 (1vs2)
2) 25-49%	22	13	9	9	
3) 50-74%	5	3	0	0	0.03 (1vs3)
MARGIN OF RESECTION					
1) > 10 mm	27	19	31	31	0.08 (1vs3)
2) < 10 mm	29	12	12	6	0.05 (2vs3)
3) No margin	12	8	0	0	
EXTRAHEPATIC DISEASE					
1) not present	56	13	22	20	0.01
2) present	12	6	0	0	
Hilum node metastases					
1) Neg biopsy	24	12	22	18	0.03
2) Pos biopsy	6	5	0	0	
TYPE OF OPERATION					
1) Wedge resection	13	17	34	22	0.06
2) Major resection	55	11	15	15	

The extent of liver involvement by tumor influenced the disease-free interval, especially when the liver involvement was 50% or more. A tumor-free margin of less than 10 mm as well as absence of extrahepatic metastases was of great importance. Patients operated with wedge resection had a longer disease-free interval than the other patients.

The following variables did not show any statistically significant variation with disease-free interval ($p > 0.15$ and no substantial difference in median values): site of primary tumor, Dukes' classification, histologic differentiation of the primary, synchronous or metachronous metastases, and liver tumor size.

The results of the multivariate analysis agreed with those of the single-variable analysis and are shown in Table 4. The following variables, arranged in order of statistical importance, were associated with early recurrence: extrahepatic disease, major liver resection, number of tumors being 4 or more, resection margin of < 10 mm, bilateral intrahepatic spread and liver tumor volume of $> 25\%$. Each variable increased the risk of recurrence 2-4 times. If the number of tumors was classified as single or multiple, instead of < 4 vs ≥ 4 , liver tumor number did not significantly affect disease-free interval. It is noteworthy, that major liver resection, as compared to wedge resection, was accompanied by early recurrence also in this analysis.

The distribution of disease with respect to the demonstrated determinants of recurrence is shown in Table 5. Patients with less than 4 tumors had a lower frequency of hepatic or hepatic-only recurrence as compared to patients with 4 or more tumors (chi-square test; $p < 0.01$ in both cases). Presence or absence of extrahepatic disease, resection margin and type of operation also varied with risk of recurrence in the liver. However, none of the variables was related to the frequency of extrahepatic recurrence.

Forty-five patients had less than 4 tumors and no extrahepatic disease. Twenty-one (47%) of these patients had hepatic recurrence as compared to 23 (100%) of the remaining 23 patients ($p < 0.001$). Development of extrahepatic metastases, however, was equally frequent in both groups, 49% and 52%, respectively.

The multivariate analysis was repeated for hepatic recurrence. The outcome was almost identical to that shown in Table 4 with the exception that the resection margin (< 10 mm vs ≥ 10 mm, relative risk 4.2; $p = 0.0002$) and the number of tumors (≥ 4 vs < 4 , relative risk 3.1; $p = 0.002$) were the two most important risk factors. In the multivariate analysis for extrahepatic recurrence, the

**Table 4. Determinants of recurrence
(Cox proportional hazards model, n=68)**

Variable	Example Status 1	Status 2	Relative Risk 1:2*	Coeff**	p-value
Extrahepatic disease	yes	no	3.9	1.37	0.0005
Type of operation	major	wedge	3.3	1.20	0.01
Number of tumors, <u>> 4</u> vs < 4	<u>> 4</u>	< 4	2.8	1.03	0.005
Resection margin, < 10 vs <u>> 10</u> mm	< 10	<u>> 10</u>	2.4	0.88	0.02
Intrahepatic spread	bilateral	unilateral	2.0	0.70	0.03
Liver tumor volume, <u>> 25%</u> vs < 25%	<u>> 25%</u>	< 25%	2.0	0.69	0.06

Included are variables with $p < 0.25$.

* A Relative Risk 1:2 means that a patient with Status 1 has a correspondingly greater risk of recurrence than a patient with Status 2, provided that all other variables in this analysis are kept constant.

** Coefficient of the hazard function.

Table 5. Distribution of recurrent disease.

Variable	Recurrence			
	Hepatic	Hepatic only	Extra-hepatic	Extra-hepatic only
Number of hepatic tumours				
< 4	31 (56)**	11 (20)**	29 (53)	9 (16)
> 4	13 (100)	8 (62)	5 (38)	0 (0)
Extrahepatic disease				
not present	32 (57)**	15 (27)	26 (46)	9 (16)
present	12 (100)	4 (33)	8 (67)	0 (0)
Resection margin				
> 10 mm	13 (48)*	4 (15)	14 (52)	5 (19)
< 10 mm	31 (76)	15 (37)	20 (49)	4 (10)
Type of operation				
Wedge resection	6 (46)	1 (8)*	7 (54)	2 (15)
Major resection	38 (69)	18 (33)	27 (49)	7 (13)
Intrahepatic spread				
Unilateral	31 (60)	13 (25)	26 (50)	8 (15)
Bilateral	13 (81)	6 (38)	8 (50)	1 (6)
Liver tumor volume				
< 25%	27 (66)	10 (24)	19 (43)	3 (7)
> 25%	17 (63)	9 (33)	15 (56)	6 (23)
Total				
	44	26	44	13

Figures within parentheses denote percentages. * = $p < 0.05$; ** = $p < 0.01$ refer to lesser risk of recurrence (chi-square test).

presence of extrahepatic disease before resection and the risk of relapse (relative risk 5.1). No other variable could be demonstrated to vary with the risk of extrahepatic recurrence.

Analysis of the survival data has been presented elsewhere (5). Briefly, the analysis indicated that resection is worth-while only when liver tumors are less than 4 (even if bilateral), no extrahepatic disease is present and a resection margin of at least 10 mm can be obtained. Factors such as type of operation (major resection vs wedge resection), uni- or bilateral disease and liver tumor volume could not be demonstrated to significantly influence survival and were not considered to help in electing or rejecting patients for liver resection.

DISCUSSION

This study showed that margin of resection, number of tumors, presence or absence of extrahepatic disease, type of operation, intrahepatic distribution, and liver tumor volume were determinants of hepatic recurrence after liver resection for colorectal secondaries. In contrast, extrahepatic disease before resection was the only variable that could predict dissemination to (other) extrahepatic sites. The liver, lungs and peritoneal cavity were the most frequent areas of failure, and all patients with relapse had disease at one or more of these sites. Ninety-four per cent of patients with relapse had intra-abdominal recurrence.

It is true that there is not much to offer a patient whose disease recurs after liver resection. However, some patients may benefit from adjuvant postresection chemotherapy, especially if effective drugs are developed. In testing existing and future drugs it is essential to know where and when the disease is likely to recur.

After operation of the primary colorectal cancer, relapse is most frequent in the liver, elsewhere in the peritoneal cavity and at the colorectal resection site (6,7). Recurrence in the liver alone is reported to occur in 4.5-19% (7,8,9). From five previous reports on resection of liver colorectal metastases, comprising a total 168 patients (10,11,12,13,14), it may be calculated that 34% of the patients had liver recurrence and that 40% of the patients had extrahepatic recurrence. Analysis of these five reports also reveals that of patients with relapse a) slightly more than half (58%) had liver recurrence, b) 1/3 had relapse in the liver alone, c) 2/3 had extrahepatic recurrence, and d) almost half of the patients (46%) had extrahepatic recurrence alone. These figures agree well with ours except that we had a higher frequency of hepatic recurrence (83% of all patients with relapse) and, accordingly, a lower

proportion of patients with extrahepatic relapse alone (17%). Similarly, liver recurrence alone or in combination with extrahepatic relapse was relatively more common in our liver resection material (36% and 83% of patients with relapse) than in the primary resection material (19% and 54%) reported by Willet et al (7). The higher frequency of liver recurrence in our patients may reflect the fact that we resected patients with relatively advanced hepatic disease. In the previous reports, about 30% of the patients had multiple liver metastases (11,12), as compared to 50% in our material.

After colorectal resection, the risk of hepatic, peritoneal and local recurrence has been demonstrated to vary with the histological differentiation of the primary tumor and Dukes' stage (7,15,16). However, those factors did not seem to play any prognostic role after liver resection. The risk of hepatic recurrence was determined mainly by the number of tumors (< 4 vs ≥ 4) and by the absence or presence of extrahepatic disease. It should be emphasized that biopsy of liver hilum lymph nodes is an important step in prognosticating the disease.

The risk of extrahepatic relapse was 50% and was not affected by the characteristics of the liver involvement or by any other variable except for the presence or absence of extrahepatic disease at the time of liver resection. Although we have some means to identify patients with a relatively low risk of hepatic recurrence, i.e. patients with < 4 liver tumors and no extrahepatic disease, about half (47%) of these patients will still get extrahepatic disease. These results have obvious implications for preoperative evaluation and selection of candidates for liver resection as well as for adjuvant treatment protocols.

Since relapse is common both in the liver and at extrahepatic sites it is rational to try to achieve effective drug levels in both hepatic inflow and systemic blood. Considering that many of the extrahepatic recurrences are situated within the abdominal cavity, intraperitoneal chemotherapy is a logical choice (17). It should be remembered that clinical series underestimate the frequency of recurrence in the peritoneal cavity unless routine exploratory laparotomy is performed and that the frequency of peritoneal surface and intra-abdominal or retroperitoneal lymph gland relapse is higher in necropsy series (8). Intraperitoneal administration would achieve high levels of the drug in the peritoneal cavity and also relatively high concentrations in the portal vein. Provided that the fractional hepatic extraction of the drug is different from zero or that the liver is not the only site of elimination, this should give a first-pass effect on the liver that makes this approach advantageous to systemic delivery also with

respect to the effect on the liver (18). In order to obtain maximal effect on extrahepatic sites, the dose chosen should give systemic levels that are close to those considered optimal after intravenous treatment.

In an adjuvant study, patients with no margin of resection, evidence of liver hilum lymph node metastases or extrahepatic disease elsewhere or patients having 4 or more liver tumors (even if diagnosed first at microscopic examination) should be excluded. It is obviously difficult to control for differences in the risk of extrahepatic recurrence. In contrast, it is possible to control some of the risk for hepatic recurrence by stratification for type of operation (major resection vs wedge resection), margin of resection (< 10 mm vs > 10 mm) and intrahepatic distribution (bilateral vs unilateral disease), in that order of priority.

The observation that major liver resection was accompanied by a higher risk of recurrence than wedge resection should be commented upon. Although it cannot be excluded that this was a result of inadequate control of nontreatment variables, it should be observed that anaesthesia and surgery has been reported to affect the immune system adversely with a risk that immunoreactivity against cancer is depressed and that dormant metastases escape destruction (19).

After resection of the primary cancer, failure at the colorectal resection site occurs in 15-63% of patients with relapse (7,9,15,16). Up to about half of the local failures (20-45%) occur more than 2 years after the primary resection (15,16), which means that the risk of local recurrence is substantial also in patients operated for metachronous liver metastases. In our material, 8 patients (15%) had recurrence at the site of bowel resection, and 5 of them had liver metastases synchronous with the primary cancer. This is an unacceptably high rate of local recurrence in patients subjected to liver resection and emphasizes the need for improved preoperative evaluation and selection of patients.

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Determinants of Survival After Intraarterial Infusion of 5-Fluorouracil for Liver Metastases From Colorectal Cancer: A Multivariate Analysis

HENRIK EKBERG, MD, KARL-GÖRAN TRANBERG, MD, PHD, CHRISTER LUNDSTEDT, MD, GUNNAR HANFF, MD, JONAS RANSTAM, BN, BENGT JEPPSSON, MD, PHD, AND STIG BENGMARK, MD, PHD

From the Departments of Surgery, Radiology, and Pathology, University of Lund, and Southern Swedish Regional Tumor Registry, Lund, Sweden

A consecutive series of 73 patients treated with intraarterial infusion of 5-fluorouracil (5-FU) for liver metastases from colorectal primary was studied retrospectively using multivariate analysis in order to find determinants of survival. Nontreatment factors had a great impact on variation in survival with liver tumor volume and metastases to lymph glands in the liver hilum as major prognostic determinants. In addition, survival from onset of treatment varied with the interval between the primary operation and the diagnosis of liver metastases. Treatment with intraarterial 5-FU was more effective when administered at long-term (3 months every 6 months) than at short-term (5 days every 6 weeks). Single temporary dearterialization, used as an adjunct to infusion of 5-FU, had a negative impact on length of survival and was followed by a high frequency of complications. The occurrence of hepatic arterial thrombosis was associated with comparatively good prognosis.

KEY WORDS: colorectal liver metastases, regional infusion, temporary dearterialization, prognostic factors

INTRODUCTION

Liver metastases are seen in almost half the patients with colorectal cancer and are of decisive importance for survival and quality of life. For nonresectable secondaries, various regimens of chemotherapy and/or liver dearterialization have been used [1-5]. With these approaches, long-term survival is occasionally seen, but the lack of appropriate controls makes it difficult to draw definite conclusions about the value of the different treatments.

The aim of this study was to describe the effects and complications of intraarterial infusion of 5-fluorouracil (5-FU), to compare a long-term and a short-term therapy, to analyze the effect of addition of temporary dearterialization, and to look for other factors of possible importance for the outcome of the patient.

MATERIALS AND METHODS

The study is retrospective and includes all the 73 patients (37 male, 36 female; median age 59 years, range 31-77) who were treated with intraarterial infusion of 5-FU at the Department of Surgery, University of Lund, Sweden, during the period April 1971-May 1981. The criteria for this type of treatment were essentially the same for the whole period, ie, regional infusion was given to every patient with nonresectable liver colorectal secondaries provided the patient had only minimal or no extrahepatic disease and was in a good general condition.

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Address reprint requests to Dr. Henrik Ekberg, Department of Surgery, University of Lund, S-221 85 Lund, Sweden

suggesting that the treatment would be well tolerated. The primary cancer was excised in all cases and no patient showed signs of local recurrence at the initiation of cytostatic therapy.

Disease Characteristics

The primary tumor was well differentiated in 1%, moderately in 92% and poorly in 7% of the cases. Three percent of the cancers were classified as Dukes' A, 44% as Dukes' B, and 53% as Dukes' C. All histologic slides were reviewed. Liver metastases were synchronous in 42 (58%) and metachronous in 31 (42%) cases. Patients with synchronous liver metastases had a notably lower frequency (19%) of extrahepatic disease than patients with metachronous metastases (39%). For metachronous liver metastases, the median disease-free interval was 20 months, being 20 months (range 5-55) for Dukes' B and 16 months (range 5-71) for Dukes' C. Additional information on the extent of tumor burden in different treatment groups is given in Tables I and II. At the time of diagnosis of liver metastases, 20 (27%) patients had pulmonary, regional lymph node, or bone metastases, or direct overgrowth to surrounding structures, such as the diaphragm. In patients undergoing temporary dearterialization, liver tumor volume as well as the frequency of extrahepatic metastases was less than in patients treated with regional infusion alone. All patients had abnormal liver function tests before therapy, and the values are summarized in Table III.

Diagnostic Work-Up

In every case, liver metastasis was verified by percutaneous needle or preoperative biopsy. Laparotomy was part of the diagnostic and/or therapeutic procedures, but it was omitted in 9 (12%) of the patients with recent primary operation. All cases were examined with hepatic arteriograms before therapy and at regular intervals during the treatment. The extent of liver involvement, in

percent of the total liver volume, was estimated by angiography and divided into four groups: less than 25% (I), 25-49% (II), 50-74% (III), and 75% or more (IV). The vascularity of the metastases was subjectively classified as low, moderate, or excessive. All angiographic examinations were reviewed. However, the angiograms for 13 patients could not be traced, and tumor volume estimation was therefore based on laparotomy findings in these patients.

Treatment

Two principally different modes of 5-FU administration were used. Long-term infusion was given at a dose of 500 mg per day for 3 months with 6-month intervals, start to start. Short-term infusion was given at a dose of 1,000 mg/m² body surface per day for 5 days every 6 weeks. The cytostatic treatment was interrupted when progression of disease was unequivocal.

Long-term regional infusion was preceded by single temporary dearterialization in 21 cases using a technique previously described [6,7] and therefore only briefly summarized here. All efferent vessels but the proper hepatic artery and portal vein were divided at the operation. Two or three days later, the common hepatic artery was occluded for 16 hours and long-term infusion of 5-FU was started after another 2 or 3 days.

During the last 6 years of the study period, patients were randomized to receive single temporary dearterialization, once it was decided that they were candidates for long-term infusion. In most cases, the choice between long- and short-term infusions was arbitrary. There was, however, a tendency that long-term infusions, with or without temporary dearterialization, were given to patients with an excellent performance status. Patients with more than a single artery always underwent laparotomy for ligation of accessory arteries to the liver.

Eleven patients received both long- and short-term infusions. In our analysis they have been included in the

TABLE I. Distribution of Disease at Onset of Therapy*

	Metastases in:				Direct overgrowth	Total No. of patients
	Liver alone	Lungs	Liver hilum	Bone		
Regional infusion, long-term	16 (67)	2 (8)	6 (25)	1 (4)	1 (4)	24
Regional infusion, short term	20 (71)	5 (18)	2 (7)	0 (0)	2 (7)	28
Regional infusion	36 (69)	7 (14)	8 (15)	1 (2)	3 (6)	52
Temporary dearterialization + regional infusion	17 (81)	1 (5)	3 (14)	0 (0)	1 (5)	21
Triple therapy from onset	19 (70)	4 (15)	3 (11)	1 (4)	2 (7)	27
No triple therapy	34 (74)	4 (9)	8 (17)	0 (0)	2 (4)	46
Total	53 (73)	8 (11)	11 (15)	1 (1)	4 (6)	73

*Figures denote numbers and, within parentheses, percentages within each treatment group.

TABLE II. Extent of Liver Replacement by Tumor*

	Liver tumor replacement					Total No. of patients
	< 25%	25-49%	50-74%	≥ 75%	Unknown	
Regional infusion, long-term	8 (33)	5 (21)	7 (29)	3 (13)	1	24
Regional infusion, short-term	7 (25)	5 (18)	9 (32)	6 (21)	1	28
Regional infusion	15 (29)	10 (19)	16 (31)	9 (17)	2	52
Temporary dearterialization + regional infusion	6 (29)	4 (19)	10 (48)	1 (5)	0	21
Triple therapy from onset	9 (33)	3 (11)	9 (33)	5 (19)	1	27
No triple therapy	12 (26)	11 (24)	17 (37)	5 (11)	1	46
Total	21 (29)	14 (19)	26 (36)	10 (14)	2	73

*Figures denote numbers and, within parentheses, percentages within each treatment group.

TABLE III. Liver Function Tests Before Therapy

	Percent pathological values	Median (range)	Normal range
Bilirubin, μ M	5.5	11 (5-100)	3-20
Alkaline phosphatases, μ kat/L	78.1	8.3 (3.1-43)	0.8-4.6
Glutamyl-transpeptidase, μ kat/L	73.5	2.5 (0.3-20)	< 1.00
Aspartate-amino-transferase, μ kat/L	42.5	0.60 (0.20-6.2)	< 0.67
Alanine-amino-transferase, μ kat/L	24.7	0.40 (0.10-4.3)	< 0.67
Carcin-embryonic antigen, μ g/l	91.9	34 (8-2,400)	< 10

TABLE IV. Number and Duration of 5-FU Infusions*

	No. of patients	Average No. of short-term infusions	Average No. of long-term infusions	Average No. of weeks on infusion
Short-term infusion	30	2.8	—	2.0
Long-term infusion	31	—	1.5	10.7
Both long and short-term infusion	11	3.3	2.0	14.0

*One patient received no infusion of 5-FU because of total hepatic arterial thrombosis immediately after temporary dearterialization.

group of long-term infusions because that was the initial, intended therapy and it also led to a higher dose of 5-FU. Table IV summarizes the number and type of infusions.

The median interval between diagnosis and onset of treatment of liver metastases was 2 months (range 0.4-21) and the period was of similar length in different treatment groups.

The hepatic arterial infusion was given via a catheter introduced surgically in 40 cases, including all 21 cases with temporary dearterialization. In 12 of these patients,

the catheter ceased to function and was replaced by a percutaneous catheter. The catheter was introduced percutaneously, if possible via the left brachial artery, in 33 patients and was later replaced surgically in four. Long-term infusion was administered through surgically and percutaneously implanted catheters in 36 and nine patients, respectively.

In addition to the regional infusion, 27 patients received vincristin (Oncovine, 1.0 mg/m² i.v.) and CCNU (100 mg/m² orally) from start of treatment and administered as single doses at intervals of 6 weeks. An average of four such treatments was given to these patients.

Most patients receiving this combined treatment (triple therapy) did not show evidence of extrahepatic metastases, but four had pulmonary deposits. In another eight cases, the triple therapy was started later (and given in an average of three cycles). Again, the reason for starting triple therapy was not obvious, but three patients had developed extrahepatic metastases.

After discontinuation of the regional infusion, 11 patients were given 5-FU intravenously, mostly for a short period. Three patients, with total thrombosis of the hepatic artery (after temporary dearterialization and regional infusion), continued with this treatment for about 2 years.

Definitions

Partial response: decrease in liver tumor volume with a duration of at least 3 months. (The volume was uniformly evaluated on angiography and compared with the examination at the time of diagnosis.) Stable disease, stationary tumor volume for at least 3 months. Treatment mortality: death within 1 month or before the patient left hospital. Survival: interval from start of treatment to death.

Statistical Methods

Therapeutic and other factors that might have influenced survival were tested for statistical significance both separately and simultaneously. Survival curves were con-

structed with the lifetable technique. The Lee-Desu test [8] was used to analyze the influence of isolated variables on survival. In the multivariate analysis, Cox proportional hazards model [9] was used to determine the importance of each variable at the same time as the influence of the other, possibly interrelated, variables was taken into account. In this analysis, all variables are entered and the variables are selected stepwise in order of importance.

RESULTS

Survival

The overall median survival time was 11 months (range 1-73) (from date of diagnosis it was 14 months). Survival was 42% after 1 year, 10% after 3 years, and 5% after five years (Fig. 1). Two patients were still alive at 40 and 54 months.

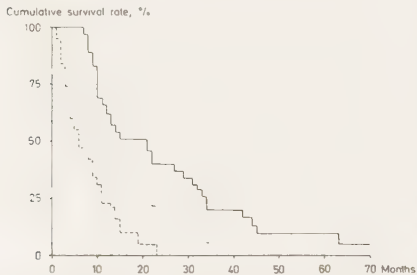


Fig. 1. Cumulative survival for all patients (....., $n = 73$), and for patients with (—, $n = 35$) and without (---, $n = 38$) partial response/stable disease. The difference between these two groups was significant ($p < 0.0001$).

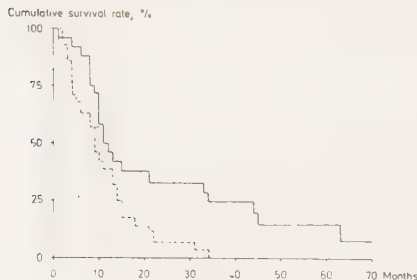


Fig. 2. The difference in cumulative survival between long-term (—, $n = 24$) and short-term infusion (---, $n = 28$) was significant ($p < 0.05$). The cumulative survival for temporary dearterialization and long-term infusion (....., $n = 21$) was not significantly different ($p > 0.05$) from that after long-term infusion alone.

TABLE V. Variables Studied in the Single-Variable and in the Cox Multivariate Analyses

Variable	Definition
Sex	Male or female
Age	Years
Site of primary cancer	Colon or rectum
Dukes' classification	A, B, or C
Interval primary operation—liver metastases	Months
Number of liver tumors	1, 2, or ≥ 3
Degree of vascularization	Low, moderate, or excessive
Liver tumor volume	$< 25\%$ (I)– $\geq 75\%$ (IV)
Liver hilum metastases	Yes or no
Pulmonary metastasis	Yes or no
Bone metastases	Yes or no
Direct overgrowth of tumor	Yes or no
Bilirubin	Laboratory value
Glutamyl-transpeptidase	Laboratory value
Alanine-aminotransferase	Laboratory value
Aspartate-aminotransferase	Laboratory value
Alkaline phosphatases	Laboratory value
Interval diagnosis—onset of therapy	Number of months
Temporary dearterialization	Yes or no
Regional infusion, length of cycle	Long or short
Catheter dislocation	Yes or no
Total hepatic arterial thrombosis	Yes or no
Partial hepatic arterial thrombosis	Yes or no
Development of pulmonary metastasis	Yes or no
Combined treatment (triple therapy)	Yes or no

Determinants of Survival Tested Separately

Table V lists all the variables that were tested for prediction of variation in survival. The following results were obtained when each single variable was tested for differences in survival without regard to possible covariation with other variables.

Treatment Factors. Excluding patients with single temporary dearterialization, long-term regional infusion was accompanied by a significantly better prognosis than short-term infusion ($p < 0.05$; Fig. 2). The addition of temporary dearterialization to long-term infusion did not result in a significant difference in survival (Fig. 2), whereas the occurrence of hepatic artery thrombosis was accompanied by a better prognosis ($p < 0.001$; Fig. 3). Patients receiving triple chemotherapy did not fare better or worse than those without, regardless of when it was started.

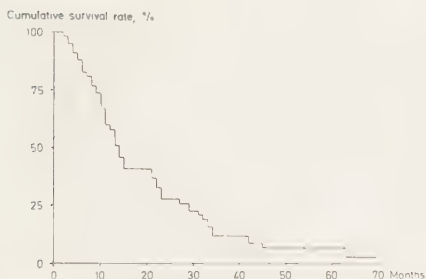


Fig. 3. The cumulative survival for patients with partial or total hepatic artery thrombosis (—, $n = 43$) was significantly longer ($p < 0.001$) than that for patients without thrombosis (---, $n = 30$)

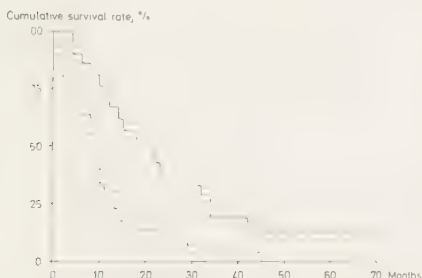


Fig. 4. Cumulative survival according to liver tumor replacement <25% (—, $n = 21$), 25-49% (····, $n = 14$), 50-74% (---, $n = 26$) and ≥75% (-·-·-, $n = 10$). The difference was significant in pairwise comparison of <25% and 50-74% ($p < 0.001$), 25-49% and 50-74% ($p < 0.05$) and <25% and ≥75% ($p < 0.05$).

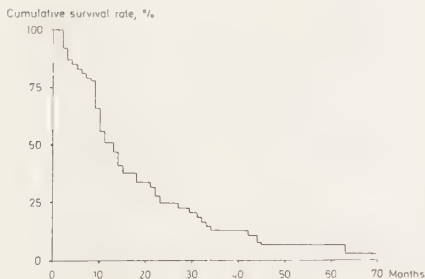


Fig. 5. The cumulative survival for patients with extrahepatic metastases (····, $n = 20$) was significantly shorter ($p < 0.01$) than that for patients without extrahepatic metastases (—, $n = 53$).

Nontreatment Factors. It can be seen in Figure 4 that the larger the liver tumor volume the shorter the survival, the difference between groups I and III being highly significant ($p < 0.001$). Patients with established extrahepatic tumor growth when the liver metastases were detected had a worse prognosis than patients without extrahepatic disease (Fig. 5; $p < 0.01$). Pulmonary metastases developed in a third of the patients during treatment, but this was without demonstrable influence on survival ($p > 0.05$).

The following factors had no statistically significant relationship to survival: number of liver tumors, degree of vascularisation, synchronous versus metachronous liver metastases, histologic differentiation of the primary tumor, or Dukes' classification. It may be noted that there was a surprisingly small variation in the histologic differentiation (see above).

Determinants of Survival—Multivariate Analysis

Since the prognosis of liver metastasis is likely to be influenced by variables that vary with each other, multivariate analysis is necessary for determination of the relative importance of these variables. For the same reason, multivariate analysis is more valid and reliable than single-variable analysis in determining the effect of treatment, because the influence of nontreatment factors can be accounted for. Table VI shows all the significant prognostic variables.

Nontreatment Factors. Metastasis to lymph nodes in the liver hilum was found to result in an eightfold increase in the risk of dying. Likewise, the extent of the disease in the liver had a great impact on survival, eg, the relative risk of dying increased eight times when liver tumor involvement increased from less than 25% to more than 75%. Also, the patients had a comparatively poor survival when bilirubin or alkaline phosphatases were elevated or when the liver metastases were detected at the primary operation (or shortly afterwards). It is of interest that Dukes' classification of the primary tumor, the degree of vascularity, and the number of liver secondaries did not influence survival.

Treatment Factors. Long-term infusion was more effective than short-term infusion, giving about four times as great a chance of (temporary) survival. The addition of temporary dearterialization was disadvantageous, resulting in more than a sevenfold increase in the risk of dying early. Partial hepatic thrombosis favored a good prognosis almost to the same extent as liver tumor volume, liver hilum metastases and temporary dearterialization contributed to a bad prognosis.

Response

No patient had total regression of the metastases on angiography. Twenty-six patients (36%) showed partial response with a median duration of 6 months (range 3–

TABLE VI. Determinants of Survival (Cox Proportional Hazards Model, $n = 71$)

Variable	Example		Relative Risk 1:2 ^a	Coefficient ^b	p-Value
	Status 1	Status 2			
Lymph node metastasis in liver hilum	Yes	No	8.4	2.13	0.0006
Liver tumor volume	>75%	<25%	8.3	0.70	0.002
Temporary dearterialization	Yes	No	7.7	2.05	0.001
Bilirubin μM	40	20	7.1	0.10	0.002
Partial hepatic arterial thrombosis	No	Yes	5.4	1.69	0.0001
Regional infusion, length of cycle	Short	Long	3.5	1.25	0.02
Primary operation—liver metastasis, interval in months	0	12	2.4	-0.07	0.0001
Aspartate-aminotransferase $\mu\text{kat/L}$	0.7	1.4	1.9	-0.45	0.02
Alkaline phosphatases $\mu\text{kat/L}$	9.2	4.6	1.6	0.10	0.001

^aA relative risk 1:2 > 1 means that a patient with status 1 has a correspondingly greater risk of shorter survival than a patient with status 2, provided that all other variables included in this analysis are kept constant.

^bCoefficient of the hazard function.

TABLE VII. Correlation Between Partial Response/Stable Disease and Selected Variables (Pearson Correlation Coefficient)

	r	p
Partial thrombosis	0.39	0.001
Total thrombosis	0.32	0.003
Long-term infusion	0.24	0.02
Alkaline phosphatases	0.23	0.03
Liver tumor volume	-0.20	0.05
Tumor vascularity	0.14	0.2
Temporary dearterialization	-0.07	0.3
Triple therapy from onset	0.06	0.3

25). The median survival for these patients was 15 months (range 8–73). Tumor volume was stationary in nine patients (12%) with a median duration of 7 months (range 3–21). The median survival for this group was 23 months (range 9–42).

The treatment thus induced a period of regression or stationarity in 48% of the patients. The median survival for these patients was 21 months as contrasted to 7 months (range 1–24) for nonresponders (Fig. 1). Partial response/stable disease was entered into the Cox multivariate analysis and found to be a significant prognostic variable ($p < 0.02$) with 1.5 as the coefficient of the hazard function (ie, relative risk 4.5, cf. Table VI). Concomitantly, the effects of the other variables changed only slightly.

A small positive correlation was found between partial response/stable disease and long-term infusion or devel-

opment of partial or total thrombosis (Table VII). There was no correlation between response and temporary dearterialization.

Pulmonary metastases were diagnosed in four (11%) of the 35 patients while they showed partial response/stationarity of the liver disease. Bone metastases developed in one patient and local recurrence in one. During the regional infusion, altogether 14 of the 73 treated patients developed extrahepatic metastases (12 pulmonary, two bone metastases, and one in the abdominal wall). In total, after onset of therapy, pulmonary metastases were seen in 25 of the 56 patients examined with a median interval of 10 months (range 3–62) between the diagnoses of liver and pulmonary metastases.

Complications

Serious postoperative complications occurred almost exclusively in patients undergoing temporary dearterialization and are summarized in Table VIII. Two patients belonging to the temporary dearterialization group died before leaving hospital, giving a mortality of 10% for this type of treatment. One of them died 7 weeks postoperatively due to generalized disease. The other patient was reoperated 2 and 3 months after temporary dearterialization because of a subphrenic abscess and died the day after the last operation.

Three patients developed intrahepatic abscesses after temporary dearterialization and two of them were reoper-

ated for drainage 4–6 weeks later. They survived 6, 24, and 42 months, respectively.

Two patients were reoperated after 5–6 weeks because of bleeding from the gastroduodenal artery. Both underwent ligation of the artery and extraction of the catheter with an uneventful postoperative course. However, one of them died 25 days after discharge from hospital with profuse haematemesis and melena. Autopsy showed numerous mucosal erosions in the colon and a few in the stomach and duodenum.

Catheter-related problems occurred in about half of the patients and were composed of, in decreasing order of frequency, dislocation of catheter, pump failure, blockage, and bleeding at the insertion site. Pump failure was restricted to long-term infusion. Aneurysm of the hepatic artery was diagnosed in ten cases (14%); once in a patient who received infusion for a total of 32 weeks via percutaneous catheters and otherwise only in patients with surgically implanted catheters. Seven of the patients had been subjected also to temporary dearterialization. Other complications did not depend on the mode of catheter insertion and varied positively with the length of infusion. The catheter perforated the duodenum in 2 cases and sepsis occurred in 1 patient.

Partial or total thrombosis of the common hepatic artery or its two main branches was seen in 43 patients (59%). Initially, the occlusion was total in 23 and partial in 20; the partial occlusion subsequently became total in 15. As a rule, both total and partial thromboses were seen early and occurred in median 11 weeks (range 1–70) after start of treatment.

The brachial artery thrombotized in 18 (40%) of the 45 patients receiving a percutaneous catheter. This is a minimum estimation because angiography of the peripheral artery was not always performed during extraction of the catheter. One case of peripheral arterial thrombosis had to be operated.

Systemic cytotoxic reactions were not seen in patients receiving regional infusion alone. Following triple and/or intravenous 5-FU therapy, dose reductions due to thrombocytopenia (platelet count $< 100 \cdot 10^9/L$) or leucocytopenia (leucocyte count $< 3 \cdot 10^9/L$) were recorded in nine (12%) and eight (11%) cases, respectively. Complaints of abdominal discomfort, loss of appetite, and diarrhea were registered in 30% of the patients.

The possible occurrence of chemical hepatitis was sometimes impossible to distinguish from changes induced by progression of the disease. Using elevation of liver function tests in patients showing partial response or stable disease as a criterion of toxic hepatitis, no patient showed signs of liver cell damage in connection with the infusion.

DISCUSSION

This study demonstrated that length of survival was negatively influenced by liver tumor volume, metastases

to the liver hilum and, to a lesser extent, by the presence of overt liver metastases at the time of the primary operation. It also demonstrated that prolonged continuous hepatic arterial infusion of 5-FU is better than intermittent treatment for a few days and that it is disadvantageous to add single temporary dearterialization prior to the infusion therapy.

The multitude of factors affecting the outcome in liver secondaries makes it difficult to determine the effect of treatment. As demonstrated in this and other studies [10–14] the influence of nontreatment factors is strong and probably stronger than that of treatment for variation in survival. Proper stratification is thus essential for making a prospective, randomized study of cytostatic therapy as effective as possible. In a retrospective study, control, though less powerful, of prognostic determinants may be obtained with the Cox multivariate regression model, which enabled us to compare treatment modalities and to select the “best” treatment for a prospective study.

Previous reports have evaluated possible prognostic determinants by looking at one variable at a time [10–12]. In the only multivariate analysis reported hitherto, Fortner et al [13] found, as we did, lymph node metastases and percent hepatic replacement to be most important prognostic factors. We found extrahepatic tumor to carry a bad prognosis when situated in lymph nodes in the hepatoduodenal ligament but not when in the lungs. The role of the latter might have been overshadowed by an advanced liver disease. Our findings agree with some reports and disagree with others. For instance, extrahepatic intra-abdominal metastases have been reported to have no [11] and pronounced [12] effect on survival. Although such differences are likely to reflect differences mainly in patient selection and statistical methods, they emphasize the need for proper staging of the disease. Whereas pulmonary metastases are known to play an ominous role, the importance of intra-abdominal lymphatic spread has not been acknowledged. Our results indicate that routine sampling of lymph nodes in the hepatoduodenal ligament aids considerably in identifying patients at high risk.

The liver tumor volume, as estimated by angiography, was an important prognostic factor. This was not unexpected; many previous reports have shown the same strong negative correlation between liver tumor volume and length of survival [10–14]. In contrast with other reports, we could not, however, find any correlation between number of tumors or tumor vascularity and survival [12,15]. The values of standard liver function tests varied with tumor volume (data not shown). In the multivariate analysis elevation of bilirubin or alkaline phosphatases showed a negative correlation with survival, independent of the concomitant increase in liver tumor volume.

Like Goslin et al [12], we found no difference in survival between patients with metachronous and syn-

chronous liver metastases when the lifetable technique was used. However, with disease-free interval as a continuous variable in the multivariate analysis, it could be demonstrated that the prognosis for patients with metachronous metastases was slightly, but significantly, better.

The histologic differentiation of the primary tumor has been reported to be prognostically important [12]. We could not confirm this, presumably because the variation in differentiation was too low. Since it is meaningless to test the influence of a variable that does not vary, the degree of differentiation was excluded from the Cox analysis.

Prolonged regional infusion had a significantly better effect on survival than pulse infusion. To our knowledge, the superior efficacy of prolonged infusion has not been demonstrated before. However, it is not unexpected while colorectal cancers have comparatively long doubling times, which means that only a small fraction of the tumor cells will be actively replicating and thus responsive to an antimetabolite like 5-FU if the duration of treatment is short [16]. The optimal length of infusion with respect to response, survival, and quality of life is yet to be determined. In this study, the prolonged infusion therapy was frequently interrupted because of arterial thrombosis with a consequent average length of infusion of 10 weeks.

Figure of the hepatic artery results in liver tumor ischemia and necrosis [17], but collaterals have been shown to develop rapidly [18]. Prolongation of survival has been uncertain and postoperative mortality and morbidity significant [5,17,19]. Temporary occlusion is believed to reduce complications and to cause a smaller increase in blood flow through collaterals [6,7]. Temporary dearterialization and regional infusion was nevertheless accompanied by a worse result than regional infusion alone. Three of the 21 patients so treated died shortly after start of treatment, and two of them never left the hospital alive. In addition, the morbidity following temporary dearterialization was considerable. At least part of the negative effect of temporary dearterialization may thus be explained by the rather high incidence of severe complications (Fig. 2, Table VIII).

In contrast to the negative effect of temporary dearterialization, the occurrence of hepatic arterial thrombosis during treatment was accompanied by a prolonged survival. This correlation with thrombosis has previously been described by Patt et al [20] and Oberfield et al [21]. These two findings, prolonged survival after (unintentional) hepatic arterial thrombosis and decreased survival after temporary dearterialization, may only seemingly be contradictory. It is conceivable that arterial thrombosis will affect the growth of the tumor by occluding small arteries, whereas the temporary dearterialization leaves these vessels intact and subject to rapid resumption of blood flow from collaterals. Since temporary dearteriali-

TABLE VIII. Complications After Surgical Catheterization Alone (n = 23) and Addition of Temporary Dearterialization (n = 21)

	Catheter Alone		Temporary Dearterialization	
	n	%	n	%
Mortality			2	10
Intrahepatic abscess (Requiring reop.)			3	14
Subphrenic abscess (reop.)			(2)	(10)
Subcutaneous abscess (reop.)	1	4	1	5
Bleeding (reop.)			2	10
Aneurysm (Requiring reop.)	2	9	7	33
			(2)	(10)
Total no. of cases	3	13	9	43

zation leaves the small arteries unoccluded, this may also explain why it did not increase the effect of the ensuing regional infusion. One reason why thrombosis is beneficial may be the resultant decrease in blood flow, which should give a prolonged drug exposure. If so, pre-existing differences in hepatic arterial blood flow may contribute to the correlation between thrombosis and survival. Considering that 5-FU causes damage also to vessel walls, it is possible that the occurrence of thrombosis signals a comparatively high concentration of the drug in a patient with a low hepatic arterial blood flow.

In this study we could not determine whether the regional 5-FU therapy was beneficial or not. The positive correlation between response/stable disease and length of survival suggests that it was, but comparison of survival rates with those of untreated patients [12,22,23] indicates that the effect of treatment was at most moderate. This issue can be resolved only by a prospective, randomized study with proper stratification of treated and untreated patients.

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**INTRAPERITONEAL INFUSION OF 5-FU
IN LIVER METASTASES
FROM COLORECTAL CANCER**

Henrik Ekberg, MD, Karl-Göran Tranberg, MD, PhD, Bo Persson, MD, Bengt Jeppson, MD, PhD, Lars-Göran Nilsson, BSc, Torbjörn Gustafson, MD, Karl-Erik Andersson, MD, PhD, Stig Bengmark, MD, PhD.

From the Departments of Surgery, Clinical Pharmacology, and Diagnostic Radiology, Lund University, Lund, Sweden.

Correspondence:
Henrik Ekberg, M.D.
Department of Surgery
Lund University
S-221 85 Lund
Sweden

ABSTRACT

Intraperitoneal 5-fluorouracil (5-FU) was given to 8 patients with unresectable colorectal liver cancer and to one patient after radical hepatectomy. A subcutaneous intraperitoneal access device was implanted, and treatment consisted of continuous infusion of 1,000 mg 5-FU/d for 5 days and was repeated every 6 weeks. Evaluation of treatment was performed after every 2 cycles of therapy. A total of 32 infusion cycles were given. The mean steady-state concentration of 5-FU was $0.56 \pm 0.04 \mu\text{mol/l}$ (mean $\pm$ SEM), and the total body clearance was $10.0 \pm 0.7 \text{ l/min}$ (mean $\pm$ SEM). The levels of 5-FU in peripheral venous blood were stable and reproducible. When incubated in whole blood at 37°C the concentration of 5-FU fell rapidly and after 2 h only 22% of the starting level remained. When kept ice cold 5-FU samples were stable. Patient acceptance was excellent, and the therapy was free from complications except for slight abdominal discomfort, not requiring alleviation by analgetic drugs. Computed tomography showed stationary tumor volume after 2 cycles of therapy in 4 of 8 evaluable patients. It is concluded that continuous intraperitoneal infusion of 5-FU produces stable and reproducible levels of the drug in peripheral venous blood, that 5-FU is degraded by blood cells at 37°C , that the use of a subcutaneous access device makes the delivery easy and safe and that the efficacy of the therapy seems to be similar to that obtained with hepatic arterial infusion.

Key words: colorectal liver metastases, intraperitoneal infusion, subcutaneous portal, 5-FU assay

INTRODUCTION

The therapeutic advantage of intraperitoneal drug administration depends mainly on a high rate of systemic clearance in combination with a relatively slow rate of peritoneal clearance (1-3). Since compounds administered intraperitoneally are absorbed mainly through the portal circulation (2,4) a significant first-pass effect in the liver is to be expected. The rate and severity of complications as well as the effort and costs involved are potentially much lower than that of other regional drug delivery approaches such as the hepatic arterial infusion modality (5).

Theoretically, intraperitoneal chemotherapy is an attractive approach for treatment of patients with hepatic and/or intraperitoneal secondaries from colorectal cancer. 5-fluorouracil (5-FU) is generally considered as the drug of choice for cytotoxic treatment of colorectal cancer (5) and fulfills the pharmacokinetic requirements of intraperitoneal delivery (2,6). Because of the predominant spread of colorectal cancer to sites within the abdomen, adjuvant intraperitoneal 5-FU has been tried in patients with advanced primary colorectal cancer (7). However, the treatment had no apparent effect on survival or time to relapse. The technique used was furthermore associated with an appreciable, and potentially avoidable, rate of complications (7,8). Data on treatment effect of intraperitoneal 5-FU on established disease is limited (9,10).

Pharmacokinetic data following continuous intraperitoneal infusion of 5-FU are sparse (10). Only a few of the 5-FU assays are sensitive enough to measure, with acceptable accuracy, the low plasma levels obtained at constant intraperitoneal infusion. The accuracy depends not only on the analytical method but also on the stability of the sample during the time between sampling and analysis. Although there are no reports on 5-FU degradation in whole blood, this must be considered a potential source of inaccuracy in the measurement of a drug with such a high plasma clearance as 5-FU.

The aim of this preliminary study on intraperitoneal 5-FU was to evaluate its effect on liver colorectal secondaries, to set up an analytical method for 5-FU determination in order to get baseline pharmacokinetic data and to evaluate the safety and ease of this kind of treatment.

MATERIALS AND METHODS

Patients

Nine patients with biopsy-proven liver metastases from resected colorectal cancer were investigated. Four of them were male and 5 female; the median age was 59 (range 45-73) years. Body weights ranged from 44 to 73 kg (median 62 kg).

Six patients had bilateral, multiple deposits in the liver at the time of the primary operation, whereas 2 patients had developed multiple tumors in the remaining liver after hepatic lobectomy. Except for one patient who received adjuvant treatment after extended right lobectomy for colorectal liver secondaries, the patients also had extra-hepatic disease: lymph node metastases in the hepato-duodenal ligament (4), peritoneal surface deposits (2), excised ovarian metastases (1), and pulmonary metastases (2).

Catheter Placement and Management

The subcutaneous intraperitoneal access device (Travenol Europe, Brussels; constructed by the present group, Fig. 1) was implanted under general anaesthesia. The infusion portal of silicone rubber was placed laterally to the left, or right, border of the rectus abdominis muscle at, or slightly above, the level of the umbilicus. The 6-7 cm long skin incision was slightly convex outwards and was extended down to the abdominal fascia. The portal was placed medial to the skin incision and was fixed to the fascia by polyglycolic acid (Dexon^R) sutures. A separate 2 cm long midline incision

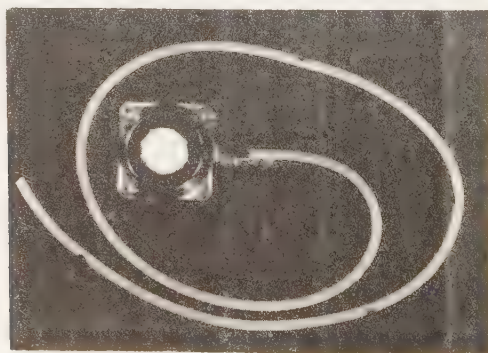


Fig. 1.
Subcutaneous intraperitoneal access device (Travenol Europe, Brussels).

was then made closely below the umbilicus. A subcutaneous tunnel between the two incisions accommodated the silicone catheter (I.D./O.D. = 0.8/2.3), of which one end was connected to the portal and the other introduced into the abdomen for a distance of about 10 cm.

After penetration of the silicone rubber septum, the infusion system was flushed with 5 ml of heparinized saline (100 IU heparin/ml). Meticulous hemostasis was assured and the incisions were closed with interrupted sutures, polyglycolic acid for fascia and monofilament polybutester (Novafil[®]) for skin.

Antibiotic prophylaxis was given only in connection with the surgical implantation. It consisted of 160 mg of trimethoprim and 800 mg of sulfamethoxazole (Bactrim[®], Roche) and was administered shortly before and during the operation as a continuous infusion in 1000 ml of 5% dextrose. Before closure, the wounds were also irrigated with 400 mg gentamicin (Garamycin[®], Schering Corp.) in 10 ml saline.

All handling of the insertion site and external catheters was done with a strict aseptic technique. Only 22 gauge Huber point needles were used for access to the subcutaneous portal. The infusion line was attached to a needle bent at 90° so that the hub of the needle lay parallel to the skin when inserted. The needle and tubing were secured in place with Steri-Strips[®] (3M Corp.) and an occlusive dressing of gauze and self-adhesive fabric (Mefix[®], Mölnlycke, Sweden). The dressing was left unchanged during the 5-day infusion period. After discontinuation of the infusion, the portal was flushed with 3 ml of heparinized saline. The needle was then removed without further maintenance of the insertion area. The subcutaneous access device was not flushed between treatment periods.

Treatment Protocol

Treatment was started 4-14 days after catheter placement. 5-FU was given every 6 weeks as a continuous infusion of 1000 mg/d (approximately 15 mg/kg/d) for 5 days. Criteria for discontinuation of treatment consisted of complications caused by therapy or progressive disease. Evaluation of treatment effect on hepatic metastases was performed after every 2 cycles of therapy. It was based on clinical examination and computerized tomography (CT) scan and/or ultrasonography of the liver and utilized criteria for response presented elsewhere (11).

Before every course of chemotherapy, a nuclear scan with intraperitoneal ^{99m}Tc-Technetium sulfur colloid (TcSc) was performed in order to ensure distribution to the entire

peritoneal cavity. The subcutaneous portal was injected with 50 MBq TcSc, particle size 1 μ m, in 0.1 ml saline solution, and immediately flushed with 3 ml saline. Gamma camera scanning was performed in the prone position after 1 h of ambulation.

If distribution was limited, an intraperitoneal infusion protocol without 5-FU was started. Repeat TcSc scans were done 2 and 24 h later, and the infusion proper (with 5-FU) was started if any of these demonstrated complete intraperitoneal distribution.

Based on the protocol worked out by Gyves and colleagues (10), 1500 ml of lactated Ringers solution was infused into the peritoneal cavity over 90 min. Subsequently, a lactated Ringers solution containing 1 g of 5-FU and 500 IU of heparin per 1000 ml was infused. The solution was given by constant, continuous infusion at a rate of 42 ml/h (1000 ml/d) for 5 days.

Peripheral venous blood (5 ml) for determination of 5-FU was obtained 2 h after start of chemotherapy, at 7 a.m. and 7 p.m. during days 2-5, and 0, 30 and 120 min after discontinuation of the infusion. Blood was collected in tubes containing EDTA. Plasma was separated rapidly and stored at -20° C until assayed. Leucocyte and platelet counts were determined daily and liver function tests at days 3 and 5 during the treatment period.

Assay of 5-FU

5-FU was measured by a modification of earlier described liquid chromatography methods (12,13). 5-FU was extracted with ethyl acetate from a 0.5 ml sample after addition of 5-bromouracil (5-BrU) as internal standard. After evaporation of the organic phase, the residue was dissolved in ammoniumacetate buffer, pH 10.2. After filtering (Bioanalytical Systems MF-1 Microfilter with RC 55, 0.45 μ m filters) an aliquot was injected onto the HPLC column. Blank plasma with known amounts of 5-FU added were taken through the whole procedure and used as standards. The HPLC system consisted of a Waters M6000A pump, a Waters WISP automatic injector, a 15 cm column packed with Spherisorb ODS 2, 3 μ m, and a Waters M481 or a Kratos 757 UV-detector set at 266 nm. A mobile phase of 0.05 M phosphate buffer pH 3.0 was pumped at a flow rate of 1.0 ml/min through the column, resulting in retention times of 4.5 and 11 min for 5-FU and 5-BrU, respectively.

Extraction recovery was low (about 50%) but stable. Using 5-BrU as internal standard, accurate results were obtained with an inter-assay coefficient of variation between 11.1% and 4.8% in the concentration range 0.28 - 1.49 μ mol/l.

Limit of detection varied between 0.1 and 0.2 $\mu\text{mol/l}$ depending on the condition of the column.

In order to study the stability of 5-FU in whole blood, 4 samples (2 drug-free heparinized blood samples with added 5-FU and 2 blood samples from patients during treatment) were divided into 3 portions and incubated at different temperatures: 37°C, 25°C, and in an ice/water mixture. After various times, aliquots were taken of which one portion was immediately frozen on dry ice and the rest centrifuged for 10 min at 1,000 g to separate plasma. The blood and plasma samples were analysed as described above with the exception that separate blood standards were used for the blood samples. Stability of 5-FU in plasma was studied in a similar manner.

Calculations

Total body clearance, TBC, (l/min) was calculated as $\text{TBC} = I/c_{ss}$, where I ($\mu\text{mol/min}$) is the constant infusion rate of 5-FU and c_{ss} ($\mu\text{mol/l}$) is the steady-state concentration of 5-FU in peripheral venous plasma. Constancy of plasma levels of 5-FU was evaluated by analysis of covariance using all values obtained on days 2-5.

RESULTS

The median number of infusion cycles per patient was 3 (1-7), and the total number of infusion cycles was 32.

Abdominal Scintigraphy

Of the 32 intraperitoneal scans performed, 30 showed a normal intra-abdominal spread (Fig. 2), whereas 2 showed an asymmetric distribution of activity. In these 2 patients, a fairly free distribution of activity was seen at repeat scintigraphy after 24 h intraperitoneal infusion of Ringers solution (Fig. 3 a,b).

Effect of Treatment

Four patients had no response and were given 2 cycles only. Two patients had equivocal evidence of progressive disease at the first treatment evaluation and an excellent performance status. Treatment was given to these 2 patients for 2 and 5 more cycles, respectively, until decisive progression. In 2 patients CT showed stationary tumor volume after 2 and 4 cycles, respectively. However, after a further 2 cycles progression was demonstrated with a consequent discontinuation of treatment. One patient received 7 cycles of adjuvant 5-FU after liver resection and did not show recurrent disease.



Fig. 2.
Abdominal scintigraphy. Normal distribution of radionuclide tracer in the peritoneal cavity 1h after injection (anterior projection). Symphysis: single arrow; diafragm: double arrows.



Fig. 3 a (left) and 3 b (right).
a) Activity trapped in an intra-abdominal pouch (open arrow) with no activity outside the infusion system.
b) Fairly free distribution 1 day later in the same patient after distention of the abdomen with fluid (see Treatment Protocol). Symphysis: single arrow; diafragm: double arrows.

Stability of 5-FU in Blood and Plasma

During incubation of whole blood at 37°C and 25°C, the concentration of 5-FU fell rapidly (Fig. 4). After incubation for 1 h at 37°C and 25°C, 5-FU in blood and plasma fell to 46% and 69% of its initial value, respectively. The decrease seemed to be of first-order with a half-life of 57 and 150 min, respectively. When kept ice-cold, blood 5-FU was rather stable. The initial blood concentrations ranged from 0.36 to 1.86 $\mu\text{mol/l}$ (median 0.62 $\mu\text{mol/l}$). The plasma/blood ratios of 5-FU varied only slightly between samples and throughout the incubations (mean 1.07, SD 0.145, $n=24$).

In plasma, 5-FU concentrations were much more stable. The decrease was less than 5% when plasma was incubated at 37°C for 4 h or at 4°C for 3 days.

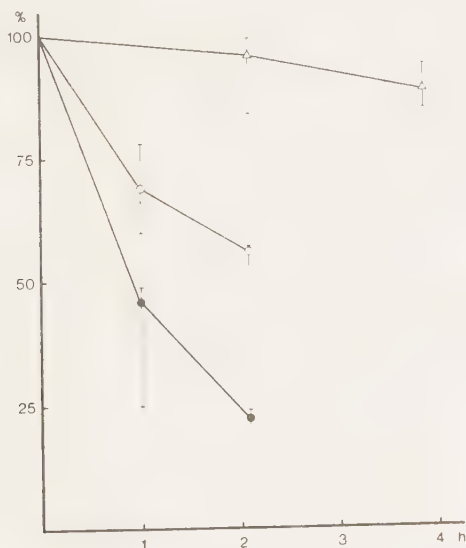


Fig. 4.

Blood concentration of 5-FU in per cent of its initial value after incubation for various times at different temperatures; ● 37°C, ○ 25°C, △ ice/water mixture. Values are medians and ranges of 4 incubations at each temperature.

Levels of 5-FU

Individual plasma levels of 5-FU are given in Tables 1 and 2. The average steady-state concentration in venous plasma (c_{ss}) was $0.56 \pm 0.04 \mu\text{mol/l}$ (mean $\pm$ SEM) (Table 3). The coefficients of variation for the steady-state concentrations varied from 12% to 39% with a mean value of 25%. Total body clearance (TBC) averaged $10.0 \pm 0.7 \text{ l/min}$ (mean $\pm$ SEM). When changes in plasma levels of 5-FU were analysed against time for days 2-5, a small, but significant increase ($0.04 \mu\text{mol/l}$) in mean steady-state values was found (analysis of covariance; $p < 0.01$). Morning and evening values did not differ.

Table 1. Concentrations of 5-FU ($\mu\text{mol/l}$) in peripheral venous plasma.

Pat no.	2 h	Day							
		2		3		4		5	
		7 a.m.	7 p.m.	7 a.m.	7 p.m.	7 a.m.	7 p.m.	7 a.m.	7 p.m.
1	0.14	0.48	0.48	0.37	0.47	0.32	0.30	0.45	-
3	0.22	0.27	0.55	0.41	0.48	0.40	0.46	0.62	0.68
4	-	0.41	0.53	0.81	0.66	0.96	0.59	0.98	0.43
5a*	0.24	0.46	0.48	0.29	0.44	0.32	0.54	0.40	0.44
5b	0.29	0.41	0.45	0.51	0.73	0.58	0.59	1.02	0.58
6	0.47	0.87	0.54	0.74	0.60	0.68	0.75	0.75	0.66
7a*	0.33	0.57	0.26	0.46	0.49	0.63	0.92	-	-
7b	0.24	0.53	0.58	0.47	0.49	0.43	0.58	0.59	-
8	<0.10	0.46	0.65	0.68	0.85	0.50	0.60	1.06	0.75
mean	0.25	0.50	0.50	0.53	0.58	0.54	0.59	0.73	0.59
SD	0.11	0.16	0.11	0.18	0.14	0.20	0.17	0.25	0.11

* Patients no. 5 and 7 were examined twice.

Table 2. Concentration of 5-FU ($\mu\text{mol/l}$) after discontinuation of infusion.

Pat no.	min		
	0	30	120
1	0.42	0.26	0.22
5a*	0.59	0.28	<0.10
5b	0.57	0.27	<0.10
7a*	0.80	0.52	0.39
7b	0.55	0.48	0.13

* Patients no. 5 and 7 were examined twice.

Table 3. Kinetic parameters.

Patient	Venous plasma c_{ss} (μ M)	CV (%)	TBC (l/min)
1	0.41	19	13.0
3	0.47	27	11.4
4	0.67	33	8.0
5a*	0.42	20	12.7
5b	0.61	32	9.6
6	0.70	15	7.6
7a*	0.56	39	9.5
7b	0.53	12	10.1
8	0.69	28	7.7
Mean	0.56	25	10.0
SEM	0.04	3	0.7

c_{ss} = Steady-state concentrations (days 2-5)
of 5-FU in peripheral venous plasma

CV = coefficient of variation

TBC = total body clearance

* Patients no. 5 and 7 were examined twice.

Complications

Patient acceptance was excellent. No infection related to the subcutaneous intraperitoneal access device or its use was demonstrated. In one patient, who had had 3 laparotomies, the treatment was discontinued due to local peritonitis. Abdominal scintigraphy was asymmetric when performed before infusion period no. 7 (Fig. 3). After repeat scintigraphy, showing a free distribution, infusion of 5-FU was started. On day 4 the patient developed localized abdominal pain and tenderness, with no fever and negative culture of the intraperitoneal fluid. The portal and catheter was extracted a few weeks later because of progressive disease.

During the week after treatment 6 patients had slight abdominal discomfort with tenderness and distension not requiring analgesia. One patient had a collection of sterile fluid around the subcutaneous portal, and start of treatment was delayed for 2 weeks.

No patient had thrombocytopenia (platelet count $< 100 \times 10^9/L$) or leucocytopenia (leucocyte count $< 3 \times 10^9/L$). Changes in liver function tests did not seem to vary with treatment periods.

DISCUSSION

This study demonstrated that continuous intraperitoneal infusion of 5-FU produces stable and reproducible levels of the drug in peripheral venous blood during a 5 day infusion period and that the use of a subcutaneous access device makes this mode of delivery easy and safe. Although the study was not primarily designed to assess the efficacy of the therapy, the effect on the liver deposits seems to be similar to that obtained with hepatic arterial infusion using a similar dose schedule (11).

The original technique used an intraperitoneal catheter protruding through the skin, which led to maintenance problems and a substantial frequency of infectious complications (8,14). The expected advantage of a subcutaneous portal in this respect was recently reported (14). Since risk of infection exists during each manipulation of the system, it is also likely that the usual dialysis exchange technique, involving frequent manipulation of the system, leads to an increased frequency of infection. The continuous infusion technique is easier to handle and involves minimal manipulation of the catheter insertion site. It is unknown if antibiotic prophylaxis is of value in connection with the implantation of the subcutaneous device. If it is, it is likely that cephalosporine is better than the regimen used in this study (14).

The rapid clearance of 5-FU by blood cells in vitro was surprising because Collins et al (6) were unable to demonstrate any transformation by human blood in vitro. The reason for the contradictory results is unclear, and direct comparison between data is impossible because Collins et al (6) did not give any details of their investigation but referred to unpublished observations. It remains to be investigated whether the metabolism of 5-FU in whole blood has any clinical consequences and whether it is anabolic or catabolic. At any rate, it means that blood samples for 5-FU should be chilled immediately in an ice/water bath, centrifuged rapidly and stored at -20°C . A delay for one hour before separation and chilling would result in a 30-50% reduction of the plasma concentration of 5-FU. Unawareness of this stability problem might account for the lower plasma steady-state levels of 5-FU reported by Gyves et al (10), as compared to those in our study (mean values of 0.34 and 0.56 $\mu\text{mol/l}$, respectively).

It may be pointed out that the rapid clearance of 5-FU is not explained by decay by blood cells in circulating blood. Using our t value of 57 min, it may be estimated that intravascular decay account for only 1-2%, or less, of the clearance of intravenously, or intraperitoneally, administered 5-FU.

It is conceivable that the regimen used in this study can be improved. The dose of 5-FU may be escalated until systemic toxicity develops (7). Escalation should, however, be cautious since our data demonstrated a small, but significant, increase of plasma 5-FU with time. As in other studies (2,6,9), this indicates that elimination of 5-FU is saturable and infers that an increase in dose may lead to disproportionate elevations in plasma 5-FU and in systemic toxicity.

Intraperitoneal delivery of cytostatic drugs may be combined with intraperitoneal instillation of compounds that potentiate uptake and cytotoxicity locally without an increase in systemic toxicity (15). It may also be combined with intermittent occlusion of the hepatic artery using another subcutaneous device (16). Improvement may also follow the use of other drugs, alone or in combination with 5-FU, and the determination of optimal positioning of the intraperitoneal catheter. We believe studies along these lines should proceed controlled, clinical studies of treatment effects.

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